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ANGIOMATOUS CONDITIONS OF THE GASTRO-INTESTINAL TRACT

BY JOHN A. SHEPHERD, LIVERPOOL

IF the publication of case records is any reflection, British surgeons appear to have taken relatively slight interest in the angiomatous conditions of the gastro-intestinal tract. The BRITISH JOURNAL OF SURGERY, for example, has recorded only 2 examples —Holman's report of a cavernous angioma of the sigmoid colon in 1948, and Rickham's recent case of multiple intestinal angiomata in a child (1952).

Confusion in nomenclature may well account for the sparse reports of such conditions. The discussion of tumours of blood-vessels is complicated by the fact that it is extremely difficult to differentiate between true tumours or angiomata and vascular malformations or 'hamartomata'. Vascular reparative tissues are at times loosely described as angiomata; highly vascular simple and even malignant mesenchymal tumours may also be inaccurately described.

It seems probable that most so-called angiomata —whatever their site—are congenital. Cutaneous nævi are noticed at birth, but those of deeper origin, although present at birth, do not attract attention until complications or chance explorations reveal them.

Histologically it is difficult to define a borderline between true angiomata and congenital malformations of vessels. The latter do not grow disproportionately with the surrounding tissues as do true neoplasms. They may enlarge, but this is explained by normal tissue growth, by accidents such as hæmorrhage, thrombosis, or inflammation, or by canalization and establishment of blood-flow to pre-existing abnormal vascular channels. Because of such tendencies vascular malformations show an infiltration of adjacent tissue and are often poorly demarcated compared with simple neoplasms. Another confusing feature is the multicentric incidence common to vascular malformations—on occasion this may simulate the metastases of malignancy.

The study of published examples of alleged angiomata of the gastro-intestinal tract supports the opinion that these are unlike true neoplasms. Solitary conditions are quite rare and in many cases some generalized angiomatous dysplasia has been present from birth.

Parkes Weber (1943) lists twenty-one vascular dysplasias under clinical and pathological features—a series ranging from the simple and probably unimportant 'ruby' spots usually referred to as 'de Morgan' spots, to the obscure and complicated lesions such as Mafucci's syndrome, where dysplasias of bone and blood-vessels combine.

From this involved but authoritative list two syndromes of particular interest to the surgeon may be selected. The first group is that of hereditary hæmorrhagic telangiectasia of skin and mucous membrane (Osler-Rendu); the second group, that of hæmangiectatic hypertrophy of limbs (Parkes Weber–Klippel). From personal experience and from other records it may be shown that such conditions present on occasion with gastro-intestinal symptoms and undergo investigation and treatment in the hands of the general surgeon.

The first two parts of this study are concerned with the two syndromes mentioned above; the third part refers to the very large group of gastro-intestinal 'angiomata' described as solitary or multiple neoplasms, but often proving on fuller analysis to be representative of some less specifically defined syndrome of vascular dysplasia. The surgical complications of these anomalies are illustrated by some examples encountered in a space of a few years. The analysis of the reported cases is not easy. The terms telangiectasia (implying dilatation of vessels from congenital, degenerative, or inflammatory causes) and angioma (implying a true benign tumour) are used indiscriminately. In this paper it is proposed to quote the original nomenclature of the authors concerned and later, in discussion, to employ the term 'angioma' without ascribing true neoplastic character.

HEREDITARY TELANGIECTASIA OF SKIN AND MUCOUS MEMBRANES

(*Syn. Osler-Rendu Disease; Multiple Hereditary Telangiectasis with Recurring Hæmorrhages; Multiple Developmental Angiomata; Hereditary Hæmorrhagic Telangiectasia*)

It is difficult to select a definition which covers all the clinical and pathological features of this disease. The title Osler-Rendu disease is retained.* The general picture of the disease is well established

* Osler published the first full account of the disease written in English. If a composite name is chosen it should really include Rendu, Chiari, and others, whose reports of the disease preceded Osler's work. Tradition has determined that Osler's name should be affixed and one other is added to distinguish the disease from those other conditions which commemorate Osler.

and it runs the following course. In childhood or in early adult life there is recurrent and troublesome epistaxis: in early or middle adult life angiomatous lesions appear on the skin—particularly of the face—and on the mucous membranes of the nose, tongue, and lips. These lesions bleed readily and may cause severe anæmia. In a large proportion of cases there is a family history. There may be, in addition, visceral lesions. The latter are of peculiar interest to the surgeon and their incidence is best revealed by a brief chronological review of some previous records of the disease.

Legg (1876) reported a man of 67 who suffered from recurrent epistaxis and had multiple cutaneous nævi. A family history was recorded and although Legg erroneously diagnosed hæmophilia this probably constitutes an early description of the disease. To Sir William Osler (1901 and 1908) we owe the first full description. Originally he recorded two families with individual members suffering from recurrent epistaxis and hæmorrhagic telangiectatic lesions of the tongue, lips, and face. Osler enumerated the varieties of skin lesions and stressed that the mucous membrane areas bled most readily. He listed previous cases described by Chiari in 1887 and Rendu (1896), and his publication led to general interest in the disease. One of Osler's patients at autopsy was found to have minor gastric lesions of a telangiectatic type.

Kelly (1906) described two cases and provided an excellent colour plate showing the facial appearance of the disease. Hawthorne (1906) described a case showing recurrent bleeding from finger-tip lesions. Parkes Weber (1907), inaugurating his numerous contributions to the subject, described one case. He stressed the coexistence of spider-like nævi on the face and nodular angiomatous skin or mucous membrane tumours. He further emphasized that both sexes are equally affected and that either transmit the disease, that anæmia is often severe and may aggravate the hæmorrhagic tendency, and that hæmorrhoids and varicose veins may be associated conditions.

Fox (1908) described a woman of 23 who at 10 had epistaxis, at 14 skin lesions, and at 23 severe recurrent rectal bleeding. Sigmoidoscopy revealed no lesion. Fox traced one other example of rectal bleeding associated with multiple angiomatous lesions on the trunk and limbs. This patient, described by Anderson in 1897, had no epistaxis and no family history. Fox was not inclined to list his case in the Osler-Rendu group as the skin lesions were almost entirely distributed on the trunk. He rejected Anderson's case also as there was no epistaxis and no family history.

Ballantyne (1908) reported three examples of the disease in one family and confirmed the familial nature. Hanes (1909) reviewed the condition fully. Parkes-Weber (1924) stressed the possibility of coexisting visceral lesions which might cause hæmoptysis, hæmaturia, or gastro-intestinal bleeding. East (1926) estimated that to date 237 individuals had been reported with the disease. He suggested that so-called 'hereditary' hæmoptysis or hæmaturia might well be an associated condition. Foggie (1928) reported a woman of 42 with fourteen years' recurrent hæmaturia. She had only one external lesion—on the lip—but belonged to a family of nose-bleeders with telangiectasia. Foggie suggested that the hæmaturia had a nævoid origin, but did not prove this.

Harper (1928) encountered a typical case with recurrent melæna. McClure and Ellis (1930) treated a patient with multiple hepatic and intestinal cavernous angiomata and with nodular cutaneous tumours resembling those of Osler-Rendu disease.

Boston (1930) described three patients with recurrent hæmatemesis. All had skin telangiectasia. The first is most instructive as operation was performed. On nævoid area was seen on the gall-bladder peritoneum. The stomach appeared normal externally and was opened; two 'nævi' which bled easily were found on the cardia. The arteries supplying the area were ligated and there was no recurrence of bleeding in a follow-up period of five years. Boston's second patient had a recurrent and fatal hæmatemesis. At autopsy an 'erosion' was seen overlying the coronary vein—no other angiomata of the intestinal tract were seen. The third case was not operated upon and gastro-intestinal lesions were not proven.

Fitzhugh (1931), in listing 4 cases, described one in detail where the following sequence occurred: epistaxis at 25, cutaneous lesions at 40, splenomegaly at 50, and melæna at 60. During life bronchoscopy and sigmoidoscopy revealed bronchial and rectal telangiectasia. At autopsy these were not confirmed and Fitzhugh suggested that visceral lesions might regress completely—an important point in prognosis and an observation repeatedly made in reference to skin lesions. Splenic enlargement he regarded as a rare and late sign of the disease. Cockayne (1933) thought splenomegaly was rare and divided the skin lesions simply into pin-point, spider, and nodular types—the latter being usually on the lips or tongue.

Hurst and Plummer (1932) recorded rectal 'nævi' in 3 patients out of 17 suffering from Osler-Rendu disease. Meikle (1933) also published a case with rectal bleeding. He described the histology of the skin lesion, noting a relative absence of muscular and elastic fibres in the vessel walls. Schuster (1937) found the disease associated with multiple aneurysms of the splenic artery. At autopsy numerous hæmorrhagic erosions were present in the stomach and first part of the duodenum. Similar lesions were also found in the pharynx, larynx, and trachea. Parkes Weber (1937) presented a man of 47 with the basic features of the disease, deformity of the little fingers, and wasting of the intrinsic muscles of the hands.*

Goldstein (1947) recorded 2 instances of severe recurrent hæmatemesis in patients with the syndrome.

Renshaw (1939) was the first to describe the gastroscopic detection of mucosal lesions. A man of 44 had a prolonged anæmia the cause of which was uncertain. He had typical telangiectases on the lip, tongue, and face. Epistaxis was frequent, but did not seem sufficient to account for the severity of the anæmia. A gastroscopy revealed multiple raised carmine spots on the gastric mucous membrane; these were similar to the external angiomata and varied in size from a "pin-head to a millet seed". No treatment was recorded.

The hæmorrhagic tendency in Osler-Rendu disease resulted in confusion with hæmophilia or purpura. The association of hæmophilia with Osler-Rendu disease was, however, belied by the different genetic behaviour of the two diseases. Davies (1939), studying 27 families with hereditary familial purpura, found only 2 with telangiectasia.

Griggs and Baker (1941) recorded 3 patients with recurrent melæna in addition to the typical basic picture of epistaxis and telangiectasia. One was subjected to laparotomy with negative findings. Penfold and Lipscomb (1943) reported a Jewish family 5 members of which had Osler-Rendu disease and elliptocytosis. Stock (1944), in reviewing the rhinological aspects of the disease, suggested an appreciable incidence of gastric involvement. Singer and Wolfson (1944) found a positive tourniquet test in one family otherwise typical—a rare purpuric association.

* While this finger deformity may merely illustrate the well-established fact that congenital conditions are often multiple, the record is interesting as in our own case of telangiectatic hypertrophy (*Case* 4) a similar defect is recorded. (*Fig.* 478.)

Gambill (1946) observed a woman of 49 with severe recurrent gastro-intestinal bleeding and Osler-Rendu disease. Visceral involvement remained unproved by operation or otherwise. In the Mayo Clinic record from 1920 to 1944 he traced 31 cases of Osler-Rendu disease none of which had gastro-intestinal bleeding.

Kushlan (1946) discussed the whole question of gastro-intestinal bleeding and gave details of a personal case. A man of 50 with a history of epistaxis, melæna, and progressive skin telangiectasia was gastroscoped. "Superficial mucosal purpuric hæmorrhages" were noted, with large branching vessels radiating to the areas; "cherry" angiomata identical with skin lesions were also seen. It was noted that the lesions multiplied distally and the small intestine was, therefore, thought to be involved. The patient was treated by transfusions and by rutin therapy. (Rutin, a vitamin-P preparation, was believed to influence capillary fragility.) Improvement was noted with regard to frequency and amount of bleeding and this beneficial result was attributed to rutin.

Markoff (1948) and Davidson (1950) were also convinced of the value of rutin therapy: Petch (1948) and Bell (1948) believed it was useless. Kennedy (1947) collected 500 individual cases of the disease from the literature—an indication that its frequency warrants a fuller recognition. Bell (1948) and Cappon (1948) further stressed that the disease is not rare.

Brandel (1950) reported a woman with recurrent hæmatemesis presumed to be due to visceral involvement.

Finally, Ashby and Bulmer (1951) recorded a woman of 63 in whom Osler-Rendu disease was associated with splenomegaly, hepatomegaly, and ascites. Melæna had occurred, but might have been due to œsophageal varices from hepatic cirrhosis rather than to gastro-intestinal angiomata.

From this review the clinical manifestations of the disease may be defined, the likely course predicted, and the lesions recognized. The incidence of gastro-intestinal involvement is shown in *Table I*, and at least 12 cases of Osler-Rendu disease have been proved to be so affected.

General Clinical Picture.—Adults of either sex present with a sequence of complaints. At or soon after puberty troublesome recurrent epistaxis develops. This may demand local investigation and measures such as cauterization of bleeding areas. Such hæmorrhages cause severe anæmia and have been fatal. Usually epistaxis recurs through life but sometimes it lessens in frequency with age. From 20 onwards, particularly in the third and fourth decades, multiple lesions are seen in the visible mucous membranes of the tongue and lips and in the skin, particularly of the face, ears, and fingers. The trunk and limbs may also be affected. Subungual involvement, according to Parkes Weber, is almost diagnostic. The vascular tumours tend to increase in number and variety with age and may bleed spontaneously or after slight trauma. Regression of individual lesions may take place, particularly after local bleeding. This general picture of Osler-Rendu disease is completed by the discovery of a strong family history. The disease appears to be developmental, almost invariably hereditary and Mendelian dominant.

In this basic form the condition is relatively innocuous, but to some cases are added visceral lesions. These are usually recognized after the cutaneous and other external manifestations are established and so affect the middle-aged or even elderly. Hæmangiomatous lesions have been reported in the stomach, upper small intestine, and the rectum. They are often assumed to be present and seldom proved at operation or at post-mortem. Rarely they may cause a fatal hæmatemesis or melæna. Spontaneous cessation of bleeding is common, with, on occasion, a regression of the individual hæmorrhagic lesions.

Hæmaturia in association with the basic features of Osler-Rendu disease is less well authenticated.

Table I.—INCIDENCE OF GASTRO-INTESTINAL LESIONS IN OSLER-RENDU DISEASE

AUTHOR	DATE	SYMPTOMS	SITE	NOTES
Osler	1901	None	Stomach	Autopsy
Fox	1908	Rectal bleeding	?	Not proved
Anderson (q. Fox)		Rectal bleeding	?	Not proved
Harper	1928	Melæna	?	Not proved
Boston	1930	Hæmatemesis	Stomach	Laparotomy
		Hæmatemesis	Stomach	Autopsy
		Hæmatemesis	?	Not proved
Fitzhugh	1931	Rectal bleeding	Rectum	Sigmoidoscopy
Hurst and Plummer	1932	Rectal bleeding	Rectum	Sigmoidoscopy
		Rectal bleeding	Rectum	Sigmoidoscopy
		Rectal bleeding	Rectum	Sigmoidoscopy
Meikle	1933	Rectal bleeding	?	Not proved
Schuster	1937	No gastric symptoms	Stomach and duodenum	Autopsy
Renshaw	1939	No gastric symptoms	Stomach	Gastroscopy
Griggs and Baker	1941	Melæna	?	Not proved*
		Melæna	?	Not proved
		Melæna and hæmatemesis	?	Not proved
Gambill	1946	Melæna and hæmatemesis	?	Not proved
Kushlan	1946	Melæna and hæmatemesis	Stomach	Gastroscopy
Goldstein	1947	Hæmatemesis	?	Not proved
		Hæmatemesis	?	Not proved
Brandel	1950	Hæmatemesis	?	Not proved
Shepherd	1953	None	Jejunum	Laparotomy
		Hæmatemesis	?	Not proved*
		Hæmatemesis	Stomach	Autopsy

* Laparotomy performed but no lesion proved.

There are 12 proved examples of gastro-intestinal involvement in Osler-Rendu disease and 13 other probable examples.

Most published cases are merely suggestive and do not withstand close scrutiny. Hæmoptysis also is rare, but has been proved to be due to angiomatous lesions in the trachea on at least one occasion. Enlargement of the spleen is uncommon and aneurysmal formations of the splenic artery may be chance associations.

Blood diseases such as purpura or elliptocytosis have been reported, and although unusual in Osler-Rendu disease, their possible coincidence must demand a complete blood investigation. Secondary anæmia from hæmorrhage may be very marked.

The possibility must arise that visceral manifestations may present *without gross external manifestations of the disease*. In such cases the diagnosis may rest on a positive family history or on the discovery of minimal external lesions following a meticulous clinical examination. Unexplained hæmatemesis, melæna, hæmaturia, or hæmoptysis may thus be elucidated.

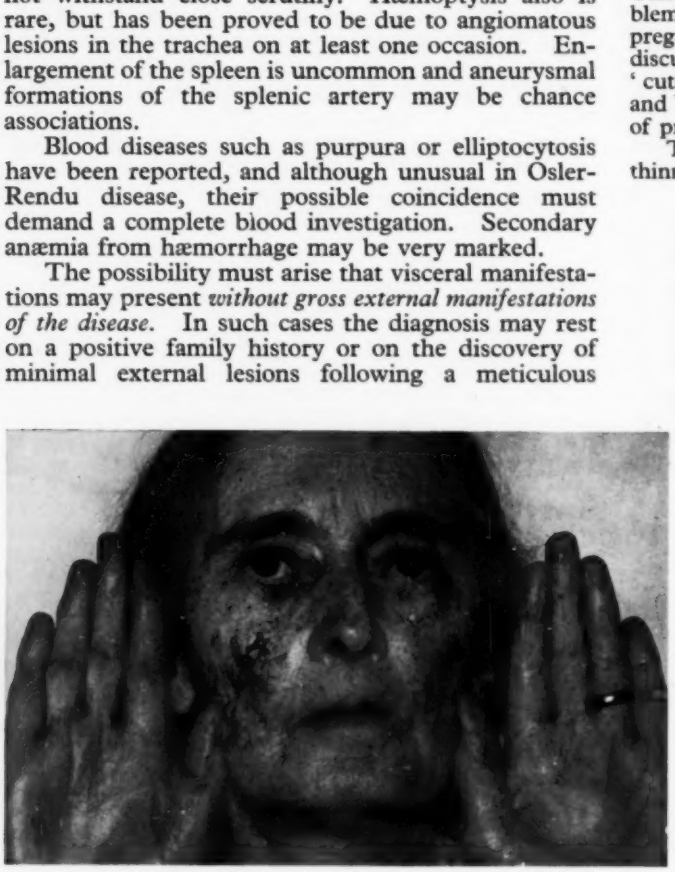

FIG. 469.—Well-marked external lesions of Osler-Rendu disease on the face and hands of a woman of 62. At present complains of severe secondary anæmia, but no evidence of external or internal hæmorrhage. A positive family history.

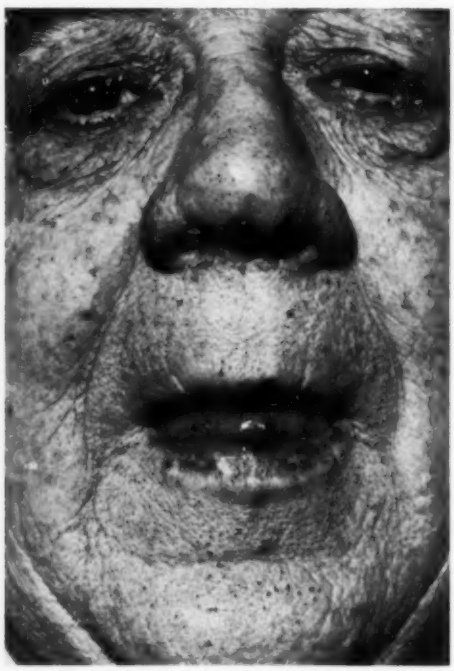

FIG. 470.—Nodular lesions of Osler-Rendu disease on face, lips, and tongue in a man of 62. Previous history of epistaxis, but no internal or external hæmorrhage at present. Family history unknown.

Character of the Lesions.—Two main types of cutaneous or mucous membrane abnormalities may present, and on their recognition will depend in most cases the correct diagnosis. These are the stellate angioma (*syn.* spider telangiectasis, spider nævus, nævus araneus, stellate nævus, spider angioma) and the nodular angioma. Lesions are also described as 'pin-point', 'mat', 'plaque', and the like. The nomenclature is confused and it is sufficient to refer to the two main types and to define them with the help of illustrations.

Stellate Angioma (*Figs.* 469, 475, 476).—This consists of a punctiform central area, flat or raised, from which radiate easily visible vessels. It is bluish or red in colour and it fades partially on pressure. Pulsation is difficult to demonstrate. It varies in size—the centre may be pin-point. It is distributed particularly on the mucosal surfaces of the lips and tongue. The skin surfaces of the nose, cheeks, ears, eyelids, and fingers—including the subungual area—are often affected. The skin of the trunk is less frequently involved. This type of lesion situated on the lower nasal mucous membrane causes the epistaxis so typical of the disease. Stellate angiomata may bleed spontaneously whatever the site.

The differential diagnosis of the stellate angiomata of Osler-Rendu disease is important as rather similar blemishes may appear in association with liver disease, pregnancy, and hyperthyroidism. Bean (1945) has discussed this question very fully in a study of the 'cutaneous arterial spider' of liver disease. Patek, Post, and Victor (1940) found such nævi in 48 out of 68 cases of proved cirrhosis of the liver.

The basic congenital or pathological change is a thinning of the vessel walls, with a deficiency of muscle tissue leading to bulging or ballooning. The defect may be enough to give rise to localized tortuous masses of such abnormal vessels.

Nodular Angioma.—This is a rather solid-looking tumour, red or cyanotic in colour, and usually lacking the 'spider legs' of the stellate type. It is 1–3 mm. in diameter and not obliterated by pressure. These angiomata are situated particularly on the lips or the tongue and on the skin of the face and the fingers (*Figs.* 470, 471, 473, 474, and 477). More rarely they occur in isolated crops on the trunk, as in a patient illustrated by Fox (1908), the skin lesions being confined to one side of the thorax. Any site may bleed, sometimes in the form of a sudden arterial spurting jet. After a hæmorrhage regression may occur, as with stellate angiomata. The nodular lesions do not fade at death, and so, unlike the delicate stellate types, can be recognized more readily at post-mortem or in tissue removed by operation. Nodular lesions may be found on visceral mucous membranes. Illustrations of such are few in number but *Fig.* 472 shows them on the serosal surface of the jejunum, while *Fig.* 471 shows the common distribution on the tongue. The occurrence of comparable angiomata on the parietal peritoneum of a boy (*Case* 4) showing hæmangiectatic hypertrophy of the limbs is interesting (*Fig.* 479).

Campbell de Morgan spots are not associated with the other features of the disease, but may resemble the nodular angiomata described above. The nodular glomus tumour

is distinguished by extreme sensitivity and its frequent location in the fingers. It is usually solitary.

The exact appearance of tracheal or other respiratory tract lesions is uncertain, but presumably multiple stellate angiomata are implied in Fitzhugh's (1931) description. The appearances of urinary tract lesions have not been accurately recorded.

The following is an example of Osler-Rendu disease with gross intestinal involvement :—

Case 1.—J. W., aged 72. The patient was admitted to hospital with a few months' history of progressive vomiting and loss of weight. He was a frail old man. A large mobile palpable mass in the upper abdomen was a grossly dilated stomach, and clinically the diagnosis of pyloric obstruction was quite apparent. One was immediately struck with the appearance of the lips and tongue and to a lesser degree with that of the skin of the face and trunk. Small bluish tumours were seen on the tongue (*Fig.* 471). These numbered about forty, and another ten were scattered along the lower lip, particularly on the inner aspect. The face—especially the nose—was profusely scattered with stellate nævi, and the trunk, particularly the chest and abdomen, was covered with Campbell de Morgan spots and flat ¼-in. diameter brownish moles. Pre-occupation with the gastric condition diverted attention from the multiple angiomatous picture, but the possibility of similar tumours in the gastro-intestinal tract was at least

FIG. 471.—Nodular lesions of Osler-Rendu disease in the tongue of a man of 72 (*Case* 1) associated with intestinal lesions. A positive family history.

envisaged. The barium meal suggested a pyloric neoplasm with gross obstruction. Operation was advised.

AT OPERATION.—A large carcinoma of the pyloric end of the stomach had spread to the cœliac glands. A palliative gastrectomy was done. On drawing up the proximal jejunum to complete the anastomosis the upper 4 ft. were found to be covered with small subperitoneal angiomata in size and appearance exactly comparable to those on the tongue and lips (*Fig.* 472). So many were present that it was impossible to choose a section of jejunum for the anastomosis without having to infringe on an angiomatous area. The tumours could be seen from the mucosal aspect, but did not project into the lumen. No angiomata were seen elsewhere on the parietal or visceral peritoneum. The liver and spleen were normal.

The post-operative course was unsatisfactory, bleeding from the anastomosis or from the traumatized angiomata of the jejunum was suspected by the aspiration of blood from the stomach tube for the next two days. The blood-loss did not seem severe, but there was a gradual collapse and death on the fourth post-operative day, despite transfusion. A post-mortem was unfortunately unobtainable.

A retrospective interest being aroused, a son was interviewed and said that his father had suffered from repeated nose-bleeding in early adult life. Two other sons and one daughter had been out of touch for many years, and as far as could be ascertained had no epistaxis or obvious external angiomatous lesions. On examination the available son was found to have three purple angiomata on his lower lip, very similar to those recorded in the father's case. Epistaxis had not been noted and there was no history suggesting gastro-intestinal bleeding.

FIG. 472.—Nodular lesions of Osler-Rendu disease on the jejunum of a man of 72. (*Case* 1.)

The son had two daughters and one of these was found to have a nævus on the abdominal wall. It was not possible to record a full genealogical table.

The appearance of the lesions, the history of epistaxis, and the inherited lip lesions in the son all seemed to justify the diagnosis of Osler-Rendu disease.

Comment.—This may be accepted as an example of Osler-Rendu disease presenting with gross intestinal involvement. It is of interest that a carcinoma of the stomach developed as in one of Osler's original cases.

The next patient illustrates the problems of diagnosis and management presented in certain cases of Osler-Rendu disease :—

Case 2.—Mrs. N. R., aged 50. This patient was admitted to hospital in 1947 with the diagnosis of pernicious anæmia. She gave a history of recurrent and severe nasal bleeding from childhood and the appearance of skin lesions in early adult life. Bleeding from small tumours on the cheek and in the mouth had been troublesome. She was noted to have occult blood in the stool, and two years later a severe hæmatemesis directed attention to the gastro-intestinal tract. A barium meal showed no obvious gastric or duodenal abnormality. In 1949 gastroscopy and sigmoidoscopy were negative. The abdomen was explored, but no visible or palpable gastro-intestinal vascular anomaly was found. Following the exploration melæna has recurred, but no severe blood-loss has troubled her.

Her family history is of interest. Of three sisters, one died of ' pernicious anæmia ', one has skin lesions similar to those observed in the patient described. Two sons have both facial and lingual lesions similar to those of the mother. One son has had recurrent epistaxis to a dangerous degree.

Her present condition is one of secondary anæmia, which accentuates the small nodular lesions seen on the circumoral skin, the mucous membrane of the lips, tongue, and palate (*Fig.* 473). A few small lesions are present on the fingers just proximal to the nail folds and the nails themselves show peculiar puckered scars under which recurrent subungual hæmorrhages have previously occurred.

Comment.—The circumstantial evidence of gastro-intestinal lesions is strong in this case. The diagnosis of Osler-Rendu disease is certain from the history, the distribution and type of the lesions, and the familial element. Here is an example of the failure not only of gastroscopy but also of laparotomy to reveal the lesions. It may be that the vascular abnormalities are entirely mucosal and invisible from the serosal aspect. It is

impossible to forecast the outcome in this patient's descendants ; one son with severe recurrent epistaxis and quite rapid accumulation of external lesions may well be at risk for the development of visceral lesions.

FIG. 473.—Nodular lesions of Osler-Rendu disease on the face, lips, and tongue in a woman of 50 (*Case* 2), associated with gastro-intestinal bleeding. Definite family history.

The third case illustrates the complications of hæmatemesis from gastric lesions and presents some unusual features :—

Case 3.—J. C., aged 54. This patient was admitted to hospital with a history of indigestion of ten years' duration. He had a 'food-pain-food-relief' sequence and after a severe exacerbation of his pain the culmination was a violent hæmatemesis. Recurrent bleeding was uncontrolled by medical treatment and on April 5, 1950, a partial gastrectomy was performed. A large duodenal ulcer was revealed as the source of hæmorrhage. About a year later bleeding recurred and a further laparotomy was performed, the development of stomal ulceration being considered a strong possibility. But there was no external evidence of recurrent ulcers in or near the gastric remnant. The duodenal stump was very adherent and actively inflamed, but duodenotomy revealed no persistent mucosal ulcer or source of hæmorrhage. The stomach was opened and a vigorous bleeding point was seen on the posterior wall—blood spurted steadily "as from a small vein" but no ulcer was seen or felt. A further cuff of stomach was excised to include the bleeding point, and the gastro-enterostomy was refashioned. In the excised cuff of stomach no lesion could be shown microscopically. The hæmorrhage ceased for two weeks and then recommenced.

On admission to another hospital on June 29, 1951, for further investigation the hæmatemesis and melæna had stopped. He was pale but not unduly anæmic, the blood-loss having been corrected by repeated transfusions. The facial appearance was striking (*Fig.* 474). Multiple nodules, 1–2 mm. in diameter, were present on and around the lips. In the region of the frænum of the tongue a cluster of larger angiomata were seen. Abdominal examination showed a recent operative wound healed by granulation. The liver and spleen could not be felt. There was no other abnormality except for trophic lesions of the tips of the fingers resembling those of an advanced Raynaud's syndrome. The blood-picture was that of a post-hæmorrhagic anæmia and the coagulation and bleeding times were normal. Liver function tests were within normal limits.

FIG. 474.—Nodular lesions of Osler-Rendu disease of the lips, tongue, and floor of mouth in a man of 54 (*Case* 3). Lesions of gastric mucosa associated.

FIG. 475.—Stellate lesions of Osler-Rendu disease observed by gastroscopy in a man of 54 (*Case* 3).

On further inquiry it was found that the right middle finger had been amputated for 'septic gangrene'. All the fingers had for the previous three winters been blue, cold, and numb, but not painful. No acute spasmodic episodes of the Raynaud type had troubled him. A prolonged jaundice had occurred six years previously after 'influenza'.

As elicited from the patient the family history was not helpful. Three members of the family were interviewed subsequently and the findings are recorded below.

Because of the exclusion of recurrent peptic ulceration at the second operation, the diagnosis of Osler-Rendu disease with visceral lesions was suggested. The facial and lingual angiomata seemed typical. Only one epistaxis had been recorded and at this stage the family

history was non-confirmatory. The possibility of the presence of œsophageal varices was not ignored, but no evidence of hepatic cirrhosis was forthcoming.

Œsophagoscopy and gastroscopy were performed. A further group of angiomata was seen far back at the root of the tongue. The œsophagus appeared normal. The gastric remnant was seen to empty well through a healthy-looking stoma. On the posterior wall of the stomach a few 'nævoid' patches were seen (*Fig.* 475). A small pool of blood lay in the stomach, but no bleeding point was detected.

On account of these gastroscopic findings and the recurrent hæmorrhages, further exploration was advised.

At Operation (July 6, 1951).—The abdomen was opened through a left oblique incision extending forward from the ninth rib. The left lobe of the liver and much of the small intestine was inspected for serosal angiomata, with negative results. The gastric remnant was buried in recent adhesions, which were separated after extending the incision for a transthoracic approach. The stomach and the anastomosis appeared normal externally. The spleen was adherent, slightly enlarged, but otherwise appeared normal. The stomach was opened by incising the anterior wall. The stoma was œdematous but not ulcerated. On the anterior and posterior mucosal surfaces of the stomach scattered angiomatous areas were seen—dark red in colour and contrasting with the pale mucosa (*Fig.* 476). Some of these lesions had been seen at gastroscopy and none showed active bleeding. Each nævoid area was cauterized with diathermy. The stomach was closed, and after freeing fresh adhesions from the afferent and efferent loops of the enterostomy the abdomen and chest were closed. A small section of liver and an affected area of stomach had been excised for histological examination.

Post-operative Course.—Three days after operation a sudden collapse occurred and blood poured from the right paramedian incision of the previous laparotomy. He died a few hours later despite transfusion.

Post-mortem Examination.—A secondary hæmorrhage had occurred deep to the right paramedian incision and had filled the peritoneal cavity with blood and ruptured the wound. The gastric mucosa showed

Fig. 476.—Stellate lesions of Osler-Rendu disease in a man of 54 (*Case* 3) observed at operation.

patchy areas coagulated by diathermy, but no other gross abnormality. No angiomatous areas were detected throughout the serosal or mucosal surfaces of the intestinal tract.

Histological Examinations.—The liver showed no cirrhotic change. The gastric mucosa taken at the operation showed no abnormality. One minute acute erosion was found in the stomach remnant inspected at autopsy.

Family Investigation.—After the patient's death it was possible to interview one brother, one sister, and a son. The brother, aged 57, was noted to have a group of angiomata situated around the frænum of the tongue. He gave no history of epistaxis or of gastro-intestinal bleeding. No other external angiomata were found.

The sister, aged 51, also had sublingual angiomata (*Fig.* 477). A small nævus was seen on the upper chest and another in the right axilla. Very faintly could be

Fig. 477.—Stellate lesions on the cheek and nodular lesions near the frænum of the tongue in a woman of 51, the sister of the patient described previously (*Case* 3).

seen a few circumoral angiomata about 1 mm. in diameter, and on the right cheek a flame-shaped telangiectatic area. She had no history of epistaxis or of gastro-intestinal bleeding. She had diabetes.

The son—the patient's only child—aged 18, had no history of epistaxis, and no external angiomata were seen.

Comment.—Despite the absence of a history of recurring epistaxis this patient may be categorized as an example of the Osler-Rendu syndrome with gastric involvement. The facial and oral lesions can be accepted. The familial element is impressive and the consistent localization of oral lesions in three members of the family is quite remarkable.

Again the difficulties of diagnosis and management are manifest. In this case the recognition of the syndrome was suggested by the classical external lesions. Gastroscopy confirmed the presence of gastric lesions. The previous discovery of a duodenal ulcer confused the history and obscured the later source of bleeding. There can be little doubt but that the more recent hæmorrhage was angiomatous in origin. The description of the bleeding point seen at the second operation is quite typical of the persistent flow from such lesions situated in skin or elsewhere. The negative histological reports are inevitable.

As treatment total gastrectomy was considered but not undertaken for two reasons. First, bleeding mucosal lesions might have been present in the small intestine, and secondly, the acute inflammatory state in the upper abdomen would have made it a precarious procedure. Cauterization by diathermy was utilized, being an application of a method eminently successful for similar lesions in the nasal mucous membrane.

The final catastrophe was due to a secondary hæmorrhage, a sequel to deep infection of the previous operative incision.

DISCUSSION

A study of the published cases shows that diagnosis of the source of gastro-intestinal bleeding in association with the recognizable picture of Osler-Rendu disease may be assisted by either gastroscopy or sigmoidoscopy. These methods of examination would locate mucosal lesions at the two extremities of the gastro-intestinal tract.

Laparotomy may reveal serosal lesions of the tract and the detection of these may suggest that mucosal involvement is also present.

Resection of the stomach or of an intestinal segment is unlikely to be justifiable. It will always be difficult to be sure that the bleeding area is being excised—multiple angiomata throughout the whole extent of the tract may often be the rule. Less radical surgery such as the ligation of vessels supplying an involved area of stomach, as adopted by Boston, must seldom be applicable. Cauterization of intragastric lesions, as in *Case* 3, seems a logical procedure.

There remains the certain benefit of blood transfusion and the uncertain value of rutin or of other drugs believed to affect capillary fragility.

HÆMANGIECTATIC HYPERTROPHY OF LIMBS

(*Syn. Parkes Weber-Klippel Syndrome*)

This condition is not easily defined but the case described below is representative. Of the numerous individuals described few are exactly comparable. The unusual problem of intestinal hæmorrhage occurred in our own case. Some of the previous records are first reviewed.

Hulke (1876) described a boy of 5 with hypertrophy of the left leg, unilateral skin nævi, and a hæmorrhagic tumour in the groin. He bled from the rectum at times. He died of infection of an ulcerated area on the groin mass. At post-mortem the abdominal aorta and the iliac arteries were said to be small and the iliac veins replaced by a plexus of small vessels. The state of the intestine is not recorded.

Reichenheim (1943) reviewed this condition in describing one new case. He referred to the numerous publications of Parkes Weber (1907 and 1943) and re-affirmed that elongation of the bones of the affected limb is combined with general tissue increase and that vascular tumours coexist in the skin or elsewhere. He noted that there is no hereditary factor and that the condition must be distinguished from hereditary œdema of the leg (Milroy's disease) and from neurofibromatous elephantiasis. Reichenheim and Parkes Weber made no reference to the possibility of visceral lesions other than the rare association of hepatic angiomata, coarctation of the aorta, and unilateral visceral hypertrophy. The case we report is unusual in this respect and only Hulke's early account of the complication of rectal bleeding has been traced. Gray (1928), Hulke (1876), and others have encountered the complication of bleeding and ulceration of superficial nævoid areas.

The clinical and pathological details of the disease are best indicated by the description of our own case. The proviso must again be made that there is no such thing as a typical case.

Case 4.—B. H., aged 7. At the age of 6 this child was referred from an orthopædic clinic to the general surgeon because of recurrent rectal bleeding associated with gross congenital limb deformation and cutaneous nævi. The family history revealed nothing which could be related to the child's condition. Father and mother were alive. The mother had always been fit and had one other child, a boy 5 years older, healthy in every way.

The child was born normally after an apparently normal gestation. At three weeks he was noticed to have diffuse soft swellings over left breast, left thigh, and right leg. Observed throughout infancy and early childhood, he was found, first, to have a progressively marked unilateral hypertrophy of the upper and lower limbs; the degree of this hypertrophy is shown in the illustration. Secondly, his mother noticed from time to time the sudden development of soft bluish subcutaneous swellings particularly on the chest and thighs—these would cause nodular swelling. Thirdly, for three years prior to the present investigation recurrent severe attacks of bleeding raised the question of a nævoid condition being present in the gastro-intestinal tract. A purpuric or other hæmorrhagic tendency was excluded by full blood examination. The general examination of the child may be summarized as follows:—

FIG. 478.—A child of 7 (*Case* 4) with hæmangiectatic hypertrophy. Asymmetry of the limbs is marked, there are scattered nævoid patches over the trunk and limbs, and the fingers show an unusual deformity. Visceral lesions were associated with these findings.

1. Average size and weight for child of 7 years.
2. Generalized asymmetrical nævoid patches on the skin of chest, abdomen, back and limbs (distribution shown in *Fig.* 478). These areas are bluish to mauve in colour.
3. Multiple areas of subcutaneous soft diffuse swellings showing slightly bluish through the skin and tender to touch. The largest are situated over the right chest and the lateral aspects of the thighs. On the thenar eminences are symmetrical lesions of a similar type. These lesions varied in size and location.

4. Deformities of the fingers shown in *Fig.* 478. Webbing at base of second and third toes on right side.

5. Relative hypertrophy of the right arm and right leg as shown in *Fig.* 478.

On these findings could be based the diagnosis of hæmangiectatic hypertrophy. It was decided that the rectal bleeding should be fully investigated in the hope that an isolated angiomatous lesion might be located and normal. (This report indicates the extreme difficulty of demonstrating an abnormality which in the living is quite prominent.)

FURTHER HISTORY.—Since operation rectal bleeding has persisted with the same frequency as before. Rutin therapy has been tried (40 mg. t.i.d.) without success. An interesting development was the appearance of thin-walled vessels branching in a stellate pattern on the surface of a rather stretched abdominal scar. These inadequately-formed vessels illustrate the child's inherent weakness in the formation of new blood-vessels.

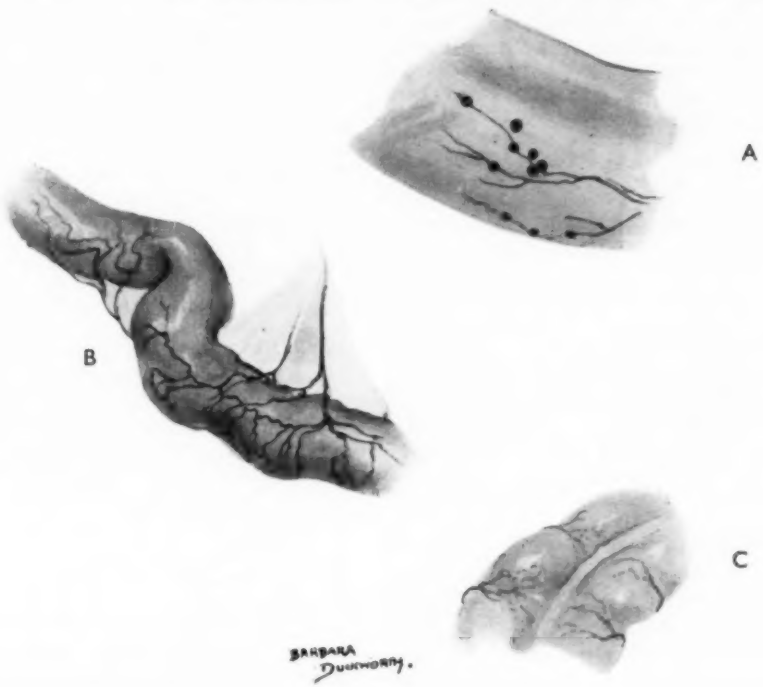

FIG. 479.—Visceral lesions in a boy of 7 with telangiectatic hypertrophy (*Case* 4). A, Nodular lesions—lateral peritoneum; B, Vascular arrangement found on serosal surface of small intestine; C, Vascular arrangement found throughout serosal surface of colon.

prove amenable to surgery. While under observation in hospital small amounts of bright red blood were passed per rectum at defæcation. Proctoscopy and sigmoidoscopy were negative and a laparotomy was thought justifiable.

AT OPERATION.—A right paramedian incision was made. Bleeding was not excessive. The following conditions were revealed:—

1. *Small Intestine*: In five segments, interspersed along the bowel, abnormal serosal vascular formations were seen. These took the form of a prominent mesenteric vessel which broke up into a tree-like formation or 'spider' form, along the branches of which were dotted small nodules. The appearance is seen in *Fig.* 479 B.

2. *Large Intestine*: The same condition occurred along the whole length of large intestine, which could be mobilized and seen (*Fig.* 479 C). The appendix showed the same abnormality.

3. On the right lateral parietal peritoneum a group of twenty-five to thirty angiomata, 2–6 mm. in diameter, were seen (*Fig.* 479 A).

No other abnormality was found. The anterior wall of the stomach and duodenum was unaffected. The liver and spleen were normal. There was no Meckel's diverticulum.

The appendix was removed.

Healing was at a normal rate and immediate convalescence uneventful.

PATHOLOGY.—The appendix was sectioned and no gross abnormality was found. The subserosal and submucosal vessels were dilated, but their structure seemed

COMMENT

The association of multiple intestinal and peritoneal vascular abnormalities with hæmangiectatic hypertrophy is shown.

It has been possible to investigate 5 other children with similar telangiectatic hypertrophies. One of these, aged 15, gives a history of recurrent rectal bleeding. Proctoscopy is negative and as there has been no recent hæmorrhage further investigation does not seem justifiable. The remaining four patients give no history of rectal or other gastro-intestinal bleeding.

In the management of gastro-intestinal complications of hæmangiectatic hypertrophy the limitations of treatment are similar to those discussed with reference to Osler-Rendu disease.

'ANGIOMATA' OF THE GASTRO-INTESTINAL TRACT

Two recognizable syndromes of angiomatous malformations have been described and illustrated. It remains to consider the incidence and characteristics of conditions of the gastro-intestinal tract which have been reported loosely as 'angiomata'

without usually being regarded as part of a generalized vascular dysplasia. Again it is convenient to summarize some of the reported cases in chronological order.

Gascoyen (1860) described a man of 44 with a large vascular tumour of the parotid, cutaneous nævi, and multiple intestinal nævi scattered along the serosal surface. Although this case is usually quoted as one of the earliest reported examples of intestinal angiomata, it seems likely from the description that it is a rare example of intestinal metastases from an angiosarcoma of the parotid. Barber (1883) reported a cavernous angioma of the rectum. Nicoll (1899) successfully resected an intussusception of the small intestine due to a single angioma. Judd and Rankin (1923) described three cases of angiomata of the stomach and one of a pedunculated angioma of the duodenum. Lockhart-Mummery (1923) observed a man with a large angioma of the rectum causing recurrent and finally fatal hæmorrhage. Brown (1924) described a stenosing type of angioma of the jejunum and reviewed 19 other cases of angiomata of the gastro-intestinal tract. Buie and Swan (1929) reported one example of a constricting angioma of the pelvic colon and another diffuse type of lesion affecting the cæcum and appendix. McClure and Ellis (1930) recorded an angioma of the jejunum associated with hepatic and cutaneous lesions. Bancroft (1931) treated a rectal angioma by injection and collected reports of 13 cases of angiomatous tumours of the colon and rectum. Buie and Nesselrod (1938) described a man of 28 with a diffuse cavernous hæmangioma of the rectum. With this was associated rectal bleeding and hæmaturia, the latter due to a similar renal lesion.

Lockhart-Mummery (1938) described an angioma involving the rectum and sigmoid colon and did not consider resection possible. Merchant (1939) encountered 2 cases of intussusception of the jejunum due to angiomatous tumours. In one of his cases multiple cutaneous nævi were present. Rankin and Newall (1933) found one hæmangioma in a series of 24 simple tumours of the gastro-intestinal tract. Pierose (1940) reported the case of a woman of 60 who had intermittent rectal bleeding for fifteen years. After two fruitless explorations a third laparotomy revealed a diffuse angiomatous condition of the jejunum which was resectable. Morton and Burger (1941) reported 2 cases of angioma of the stomach and reviewed 14 such lesions. Hunt (1941) listed a total of 48 cases of gastro-intestinal angiomata and added 1 case of a cavernous type of the sigmoid colon and rectum with involvement of the adjacent uterus. Christopher (1942) described a solitary angioma of the stomach encountered when operating for trauma. Packard (1945) resected a solitary angioma of the ileum. Polayes and Nevins (1945) recorded a fatal hæmorrhage, during pregnancy, from one of several angiomata of the ileum noted. Gabriel (1948) reported 2 cases of extensive angiomatous formations in the rectum. Lazarus and Marks (1947) found a case with multiple angiomata in the whole length of small and large intestine. (Cutaneous nævi were noted.) The colon was resected as it was believed to be the major source of bleeding. The patient was relieved of symptoms. Browne and McHardy (1947) recorded a solitary angioma of the jejunum. Holman (1948) recorded an angioma of the sigmoid colon. The patient had nævi of the tongue and hand. Hansen (1948) reported 3 examples of small intestine angiomata. Two were from post-mortem records—one an example of multiple intestinal cavernous lesions and the other of multiple intestinal lesions with generalized angiomatous changes in other viscera. The third case was an example of an acute intussusception due to an apparently solitary angiomatous mass projecting into the ileum. Hansen included his 3 cases in a review of 66 examples of hæmangiomata of the gastro-intestinal tract. He classified 27 cases under the heading ' multiple phlebectasia '—including the gastro-intestinal manifestations of Osler-Rendu disease under this title. Twenty-three cases were classified as cavernous hæmangiomata and subdivided into diffuse infiltrating and circumscribed polypoid types. Eight cases were classified as simple capillary hæmangiomata. Finally, 8 cases were examples of hæmangiomatosis localized to the gastro-intestinal tract. All 66 cases were tabulated in detail.

Rickham (1951) described a child of 10 who had recurrent melæna or frank rectal bleeding. There was a cavernous hæmangioma on the palm of the hand. Investigations proving negative, the abdomen was explored with the expectation of finding a hæmangiomatous condition of the intestine. Three small tumours were found at wide intervals along the small intestine. They projected into the lumen of the bowel and the largest was the size of a ' blackberry '. Local excisions were performed, and after operation there was no recurrence of bleeding.

Heycock and Dickinson (1951) recorded the case of a 6-year-old child who for five years had recurrent rectal bleeding. Multiple subcutaneous hæmangiomata had been treated intermittently, and because of these the diagnosis of intestinal hæmangiomata was advanced. At operation nineteen tumours varying from 2–3 mm. to 1 cm. in diameter were incised from the small intestine without resorting to resection. At a further operation another seven tumours were removed from the small intestine and others on the colon were excised by resection of a 5-cm. segment. After these two operations hæmorrhage ceased, but further local excisions are contemplated if necessary. Local resection was advocated even if minor affected areas remain. The diagnostic aid afforded by external lesions was stressed.

The examples quoted in the above survey give some conception of the incidence of gastro-intestinal angiomata. If angiomata of the gastro-intestinal tract are in any way comparable with other tumours the relative frequency is of interest. Thus Wakeley and Paul (1930) indicate their rarity and quote King as listing only 3 angiomata in a series of 118 simple tumours of the gastro-intestinal tract. Raiford (1932), from a large series of autopsies, found that only 0·05 per cent of all gastro-intestinal tumours were hæmangiomatous and other true simple tumours were much more frequent. Rankin and Newall (1933) found one hæmangioma in a series of 24 simple tumours of the gastro-intestinal tract. Pierose (1940) quotes a 1936 review by Kaijser listing 74 cases affecting the gastro-intestinal tract. Eight of Kaijser's cases were examples of generalized vascular dysplasias or ' hæmangiomatoses '. Lazarus and Marks (1947) collected only 38 cases and list these in detail. Browne and McHardy (1947) review 95 cases. Hansen's (1948) 66 cases have already been mentioned.

The discrepancies of these figures are easily explained by the wide range of conditions recorded and by a failure to differentiate between those lesions thought to be confined to the gastro-intestinal tract and those obviously associated with generalized vascular malformations.

Patients of both sexes and all ages have been recorded. Many examples have been revealed at autopsy or at incidental laparotomy. Where symptoms have occurred, the most important is bleeding. This may take the form of hæmatemesis, melæna, or frank rectal hæmorrhage. Bleeding may be torrential and rapidly fatal, but more often is intermittent or

occult and productive of a secondary anæmia which defies explanation for a long time. Obstruction from angiomatous tumours is rare and may take the form of a slow stenosis or acute blockage from a polypoid tumour with or without intussusception of the bowel.

Many attempts have been made to classify angiomatous formations in the gastro-intestinal tract. Brown (1924) gave a clinical grouping :—

1. Multiple minute tumours appearing in the vascular arcades—small nodules best seen by transmitted light.
2. Submucous tumours of varying size projecting into the lumen of the bowel.
3. Submucous tumours occluding the bowel by their bulk.
4. Diffuse mucosal tumours constricting the bowel.

To this classification we would add for completeness a differentiation between single and multiple tumours and a distinction between lesions which are apparently confined to the intestinal tract and those which are quite clearly part of a widespread vascular dysplasia.

Fraser (1919) suggested the simple pathological division of all angiomatous tumours into capillary, compact, and cavernous types. This classification can be applied to intestinal angiomata, with the addition of a racemose or varicose lesion not infrequently described in the rectum or pelvic colon.

Histological classification is difficult. The capillary nævus is composed of a meshwork of endothelium-lined channels of variable size and blood-vessels with thin walls. The compact hæmangioma has a more neoplastic appearance, as there may be solid alveolar masses of endothelial cells and less obvious blood-spaces, and appears to spread into adjacent submucous layers. It may enlarge with growth probably by canalization of pre-existing blood-spaces rather than by true neoplastic advance. The larger tumours, particularly of the rectum, may be composed of a ramification of small blood-vessels rather like a varicocele.

Histological appearances are difficult to define in the excised specimen as vessels and blood-spaces and are difficult to preserve in their original shape—even the fresh specimen of a resected angioma becomes almost unrecognizable as such when the blood-supply to the mass is cut off. Thrombosis and infection readily alter the histological appearance of these tumours and fibrosis following recurrent hæmorrhage may further confuse the picture.

Any type of angiomatous lesion may rupture and bleed, ulceration may be perpetuated, or obstructive conditions may develop. Any type may present as an apparently solitary lesion or alternatively be part of a generalized vascular dysplasia.

Malignant change in the form of angiosarcomatous formation is almost unknown. Winternitz and Boggs (1910) described a rare example of angiosarcomatous involvement of the intestine. If angiosarcomatous lesions of the intestinal tract are found these are most likely secondary to angiosarcoma elsewhere. McCarthy and Pack (1950), reviewing 56 cases of angiosarcoma and Kaposi's sarcoma, indicate, however, that intestinal metastases are rare and advanced complications.

Regression of small angiomata is much more likely than neoplastic change—as has been observed in the visceral lesions of Osler-Rendu disease.

The distribution of angiomata in the gastro-intestinal tract is difficult to assess. Fourteen cases have been reported in the stomach (Morton and Burger, 1941). About 40 cases have been reported in the jejunum. At least 20 cases have been reported in the lower colon and rectum. The ileum and upper colon are less often involved. These figures are very approximate, as it is difficult to assess the proportion of solitary lesions to multiple lesions. This would require post-mortem evidence in every case.

It is probable that the majority of cases are multiple or potentially so, and a minority are single well-defined polypoid or pedunculated lesions which may be regarded as true neoplasms. In reading the published reports of all available cases one cannot fail to be impressed with the high incidence of cutaneous lesions in association with the intestinal condition. Few authors negative skin lesions and it is possible that if the association were recognized the reported coincidence would be even higher than it is at present. The presence of cutaneous lesions does in fact give, as Rickham (1951) and Heycock and Dickinson (1951) stress, a most useful clue to diagnosis in these otherwise obscure cases.

From the practical aspect diagnosis is inevitably a problem, and may only be a matter of conjecture when other commoner causes of gastro-intestinal bleeding are excluded. Gastroscopy or sigmoidoscopy will prove helpful only in the upper and lower levels of the tract. Selective intubation (Van Noate, 1950) by suction of intestinal contents at different levels may determine the site of bleeding or even permit of refinements of radiological technique which may on occasion show up an angiomatous area. Judd and Rankin (1923) showed a single polypoid lesion radiologically, but positive findings are seldom reported by the radiologist. Even at operation the extent of mucosal involvement may be difficult to determine.

Treatment is usually decided at the laparotomy which establishes the diagnosis. If the condition after careful inspection and palpation of the whole length of the tract seems to be localized, the local resection of the tumour or the involved segment may be a simple matter. Since Nicoll's (1899) case a few successful resections for acute obstructive conditions have been recorded.

A more difficult problem arises where multiple lesions or diffuse angiomatosis is found. The actual location of the bleeding area may remain in doubt ; in fact there may be more than one source of hæmorrhage. Wholesale resection of small intestine cannot be carried out light-heartedly and each case must be weighed individually.

Diffuse rectal angiomata often attain great size and offer particular technical problems. Two-stage abdomino-perineal resection may be indicated and the mortality-rate has been high. Bancroft (1931) treated a rectal angioma in an ingenious manner by exposing its serosal feeding vessels and injecting them with sclerosant solutions to produce a thrombosis. Hunt (1941) achieved a successful two-stage abdomino-perineal resection and Babcock and Jones (1950)

describe a successful one-stage abdomino-perineal proctosigmoidectomy with preservation of the anal sphincter.

The following case illustrates some of the problems of the management of a patient with multiple angiomata of the small intestine :—

Case 5.—N. C., aged 22. This patient, a Petty Officer in the Royal Navy, complained of recurrent severe bleeding per rectum. Usually the blood was bright red and appeared at defæcation. He had no indigestion or abdominal pain. Clinical examination was negative. A full radiological investigation, gastric analysis, and blood

FIG. 480.—Multiple angiomata of the ileum in a man of 22 (*Case* 5).

estimation revealed no obvious cause. Sigmoidoscopy was negative. Laparotomy was decided upon.

AT OPERATION.—Right paramedian incision. The stomach, duodenum, and colon were normal. In the last 4 ft. of the ileum several slightly swollen areas of purplish discoloration showed through the intestinal wall These were roughly oval and varied from $\frac{1}{4} \times \frac{1}{2}$ in. to $\frac{1}{2} \times 1$ in. (*Fig.* 480). The largest area was excised locally for examination, as a complete resection of 4–5 ft. of bowel was not considered advisable. Blood-clot was seen in the lumen of the bowel. The longitudinal elliptical defect was sutured transversely and the abdomen closed. No other abnormality was detected.

The patient made a good recovery and for three months was free from bleeding. Thereafter rectal bleeding recurred and he was discharged from the navy.

Four years later he was traced and wrote to say that he had had an acute obstruction one year after the original abdominal exploration. The cause of the obstruction was uncertain. Resection of gangrenous intestine was performed and the surgeon who operated did not note any hæmangiomata of the bowel. Since this unfortunate sequel recurrent rectal bleeding has continued and causes extreme weakness at the time. It remains unassociated with other symptoms. At present he is loath to have a further operation.

The pathological section of the tissue removed at the first operation has been lost, but at the time ' hæmangioma of the ileum ' was reported.

Comment.—This case presented the usual diagnostic problem. An extensive resection might have been done, but it was thought that the whole length of the small intestine might well be involved by other less obvious angiomata. The subsequent acute obstruction may have been due to a stenosing angiomatous condition unrecognizable in the gangrenous bowel, but was more likely due to adhesions or fibrous stricture following the local biopsy. Subsequent questioning has revealed no family history of relevance and so far there is no suggestion that angiomatous lesions have appeared in the skin or elsewhere.

A further case shows the very difficult problems of diagnosis and management presented by a patient who had an angiomatous formation in the stomach.

Case 6.—A man of 34 was admitted to hospital for investigation of recurrent hæmatemesis in 1939. Radiological examination showed an ' intramural growth in the lower third of the greater curvature of the stomach—probably malignant '. The abdomen was explored and a tumour felt in the stomach and gland enlargements noted in the gastrocolic omentum. The growth was thought to be inoperable. After this operation hæmorrhage recurred and at another hospital gastroscopy revealed a hæmangiomatous area on the greater curve. In 1946 the abdomen was again explored and a total gastrectomy was performed as the condition seemed to have become diffuse. The gross appearance of the excised specimen was inconclusive and sections of the allegedly involved stomach wall showed no abnormality histologically. The patient remains alive and moderately well but under continual observation and treatment for dietary deficiencies due to faulty absorption after total gastrectomy. There has been no recurrence of bleeding. There are no external nævi.

Comment.—This is an example of a patient with an angiomatous tumour of the stomach believed by a competent radiologist to be malignant and by an experienced surgeon to be inoperable. Again revealed after a six-years' interval at a second laparotomy, the tumour was quite unrecognizable in the resected specimen grossly or microscopically.

In relation to such gastric conditions one may theorize as to the cause of unexplained severe gastric bleeding. All surgeons of experience have on occasion explored patients with severe hæmatemesis and failed to demonstrate an obvious source of bleeding. External examination, gastrotomy with internal inspection, and even examination of the fresh or fixed gastrectomy specimen have been negative. The label ' gastrostaxis ' or ' gastric erosion ' is applied. Some of these may be explained by hæmorrhage from small angiomatous conditions. Boston (1930) has suggested this possibility, and the failure of the pathologist to define any lesion in *Case* 6, described above, emphasizes the diagnostic difficulty.

We believe therefore that in any case of gastric hæmorrhage the origin of which is obscure, a meticulous search should be made for angiomatous lesions which will only be seen readily in live tissue and which may be negligible when the local circulation is cut off. Vascular lesions in other tissues may give a clue, and a family history of hæmorrhagic angiomatous conditions should be excluded.

SUMMARY

It is believed that gastro-intestinal tumours in the form of true angiomata are rare, but that malformations or defects are common as multiple conditions on the gastro-intestinal tract. Some of these widespread anomalies in the alimentary tract are part of generalized vascular dysplasias, of which Osler-Rendu disease is one important specific and recognizable type. The Parkes Weber-Klippel syndrome is a rarer association.

The diagnostic and therapeutic problems of such conditions deserve wider notice than is at present accorded to them.

This survey of a relatively neglected problem is illustrated by the description of 3 cases of Osler-Rendu disease with gastro-intestinal lesions, 1 case of telangiectatic hypertrophy complicated by intestinal lesions, 1 case of multiple ileal angiomatous tumours causing severe bleeding, and 1 lymphangiomatous tumour of the stomach presenting an extreme diagnostic and therapeutic puzzle.

This personal experience and some research into other published material indicates the frequency of such conditions, and may stimulate interest in a rather neglected subject.

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THE RESPONSE OF PROSTATIC CARCINOMA TO ŒSTROGEN TREATMENT

By J. D. FERGUSSON and L. M. FRANKS

CENTRAL MIDDLESEX HOSPITAL, THE INSTITUTE OF UROLOGY, AND THE LABORATORIES OF THE IMPERIAL CANCER RESEARCH FUND, ROYAL COLLEGE OF SURGEONS

THE object of the work reported here was to investigate the changes that occur in prostatic carcinoma after prolonged treatment with œstrogens, and this report follows a previous one (Fergusson and Pagel, 1945) which demonstrated the histological changes in a small number of cases. Clinically, after treatment there is often a decrease in size and hardness of the primary tumour and metastases, radiological evidence of resolution of secondary deposits in the bones, a lowering of the serum acid-phosphatase level, and an increase in the expected survival period. The changes that occur have been described by many authors (Huggins, Scott, and Hodges, 1941; Huggins and Hodges, 1941; Schenken and others, 1942; Nesbitt, Pazzos, and Cummings, 1944; Kahle, Schenken, and Burns, 1945; Reynolds, Schulte, and Hammer, 1950). We have now attempted to correlate these changes with the clinical picture by studying all cases in which it has been possible to examine suitable pathological material on two or more occasions from the same individual in a series of 150 consecutive cases of prostatic cancer treated with œstrogens (5–30 mg. of stilbœstrol or equivalent, daily) and followed up over a period of nine years at the Central Middlesex Hospital.

Collection of Material.—Clinically, opportunities for obtaining representative serial histological material are limited. An initial biopsy examination may be made to confirm a doubtful diagnosis, at operation for the relief of urinary obstruction, or for histological confirmation of tumour type. If the suspected tumour is small a perurethral biopsy may fail to remove tumour tissue, but with more advanced cases sufficient material for adequate examination can generally be obtained.

During œstrogen therapy tumour tissue may be removed to relieve persistent or recurrent urinary obstruction or for other reasons. Persistent obstruction is generally due to an inadequate preliminary operation, and the time interval between the two biopsies will thus be short and little change in the tumour can be expected. Recurrent obstruction may be due to the growth of an œstrogen-resistant tumour after a previous successful resection, or to the development of œstrogen resistance in a previously sensitive tumour. In both cases no histological regressive changes can be expected in view of the clinical evidence of renewed activity of the growth.

Thus the most favourable circumstances for the observation of histological changes in the tumour will be those in which substantial portions of tissue are removed at intervals during sustained œstrogen treatment from patients showing no clinical evidence of growth of the tumour, i.e., at a time when biopsy is unlikely. In addition, material suitable for comparative study may sometimes be obtained post mortem from cases who have had a biopsy in life, but the chances of this showing regressive changes are greater if the patient has died of intercurrent disease.

Other factors which may influence the comparison of material removed during œstrogen therapy are variation in dosage, unsuspected treatment with œstrogens or other drugs before the initial biopsy, and tissue reactions produced by trauma at a previous operation. For the latter reason a resectoscope of the cold-punch type seems preferable to the McCarthy instrument, as it appears to produce a less-marked local tissue reaction. Diathermy should be used as little as possible.

Lastly, it is important that fixing and staining methods should be identical for all parts of the tissues to be compared, both from the initial and subsequent material.

Any interpretation of alteration in the histological appearances must therefore take account of the circumstances under which tissue is secured, the method of removal, and the variability of structure well known to exist within a single tumour.

MATERIAL AND METHODS

Tissue was obtained by repeated biopsy or biopsy and subsequent post-mortem examination. Biopsy material was removed by a suitable needle through the perineum, perurethral resection, or open operation. Occasionally it was possible to examine repeated biopsies from accessible secondary deposits in lymph-nodes or bone. In all cases it is, of course, difficult to be certain that any tissue removed is representative of the tumour as a whole, particularly if only a small portion is available for examination.

Eighty-two specimens of carcinomatous tissue removed at biopsy or autopsy from the prostate in 33 patients were available for study. Paraffin sections stained with hæmatoxylin and eosin were examined by one of us (L. M. F.), and in some cases sections were stained for elastic tissue (Orcein), reticulin (Foot's method), or by a modification of Masson's trichrome method. The tumours were then graded (*see below*) and the presence or absence of œstrogen effects on the tumour and normal tissues (if present) were noted. After this had been done the histological results were correlated with the clinical and other findings, i.e., the microscopical assessment was dependent *only* on the histology. The clinical details were purposely withheld at this time.

Notes on Grading.—The difficulties of tumour grading are well known, and these are much increased when small fragments of tissue from a large tumour mass are available. Grading may be based on the character of the individual tumour cells (cytological differentiation), the histological arrangement of the cells (structural differentiation), or on the extent of spread (including local vascular or lymphatic involvement), and it is obvious that a low grading in one character does not exclude a higher grading in

another. In practice, therefore, the final grade into which a tumour was placed depended upon an assessment of all three factors. Thus the tumour grading could not be done with mathematical accuracy, but must remain only a personal opinion of the pathologist concerned. Again, variation in structure or response to treatment throughout a tumour mass may give a quite erroneous impression if only one area is fortuitously selected for biopsy.

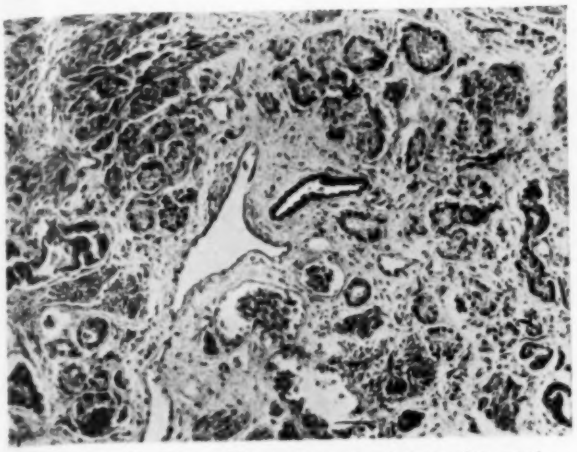

FIG. 481.—P. B. 1. No œstrogen treatment. (× 240.)

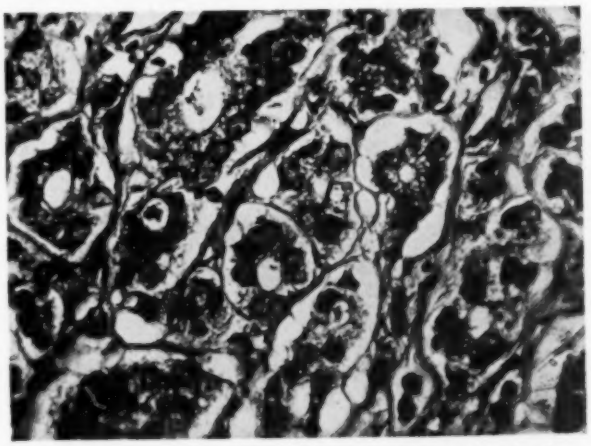

FIG. 482.—H. B. 1. No œstrogen treatment. (× 810.)

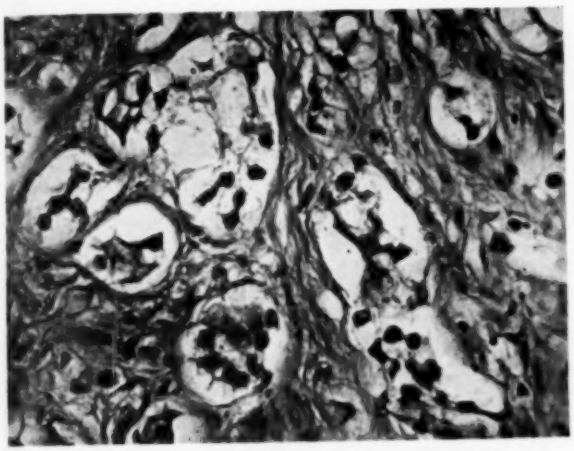

FIG. 483.—H. B. 2. Showing œstrogen effect after one week. (× 810.)

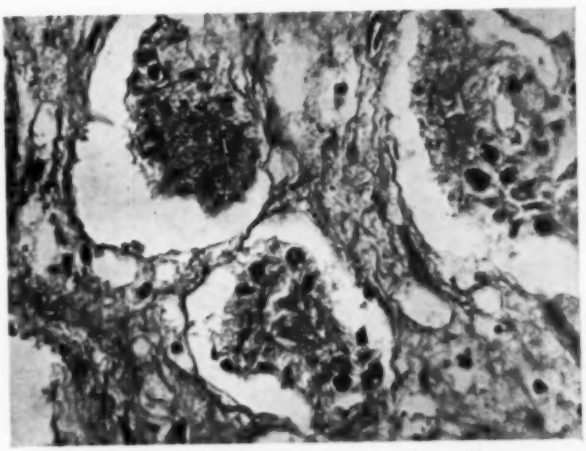

FIG. 484.—H. B. 3. Showing œstrogen effect still present after seventeen months. (× 810.)

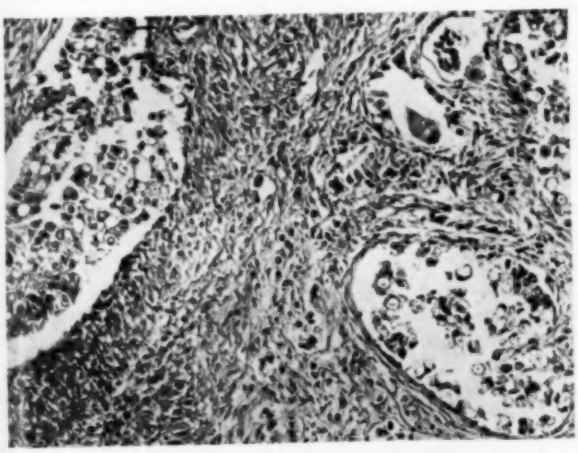

FIG. 485.—W. B. 2. Showing intracytoplasmic vacuolation and desquamation of carcinomatous cells. A post-mortem case treated with œstrogens for thirteen months. (× 300.)

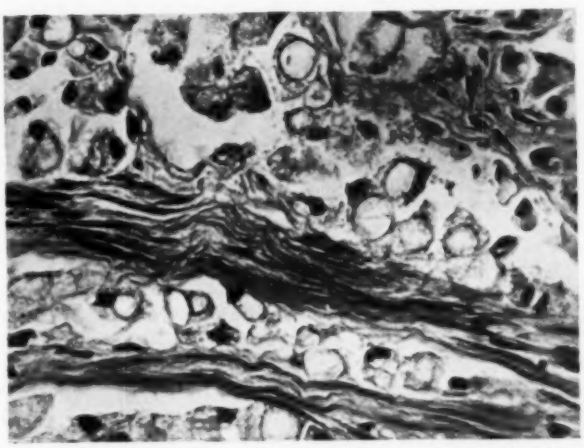

FIG. 486.—T. R. 3. Showing marked intracytoplasmic vacuolation and nuclear pyknosis. Post-mortem case treated with œstrogens for thirty months. (× 915.)

Three grades—low, average, and high—in ascending order of malignancy were used, but the striking feature in all cases was the variability of the

histological picture. As a rule there was a predominant cell type and structure, but a careful search would show almost all other types in different areas. However, it was possible to place all the tumours examined in one or other grade.

RESULTS

Cytology and Structure.—Three cell types were commonly seen—a clear or reticular cell with finely reticulated cytoplasm, a dark cell with condensed, more basophilic cytoplasm, and an anaplastic cell with a large vesicular nucleus and prominent nucleolus. There were intermediate forms between all three cell types. The structure was commonly small acinar or solid trabecular, but cribriform, anaplastic, and diffuse (individual cells in stroma) areas were also seen. Any of the above may be of either clear or dark cell type. There was no example of a definite squamous carcinoma, but one case may possibly fall into this group. Any type may stimulate a scirrhous reaction, but this was most commonly seen with the dark-cell, solid trabecular form.

Vascular involvement, mainly capillary but sometimes of small veins, was common.

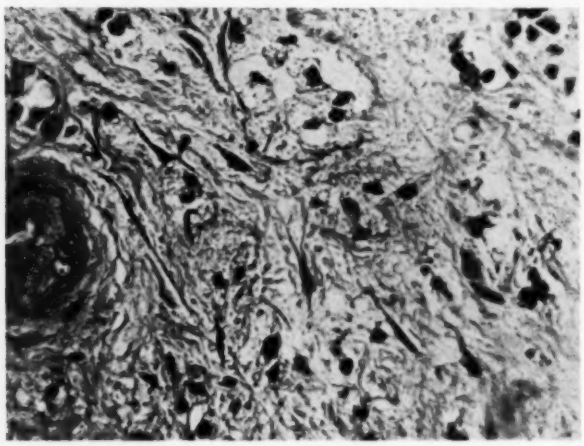

FIG. 487.—H. M. 2. Showing cytoplasmic vacuolation, nuclear pyknosis, dissolution of epithelial-stromal margins, and marked stromal changes. (× 870.)

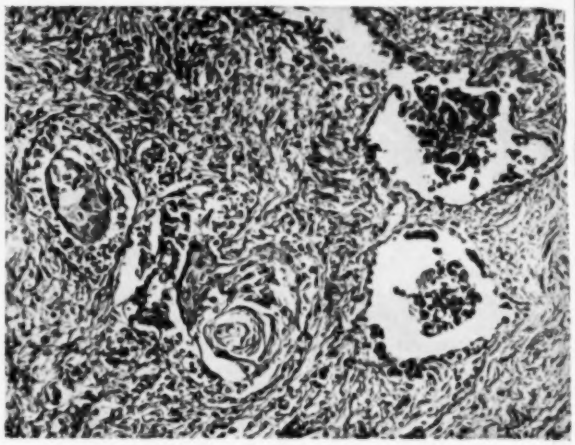

FIG. 488.—W. B. 2. Showing squamous metaplasia in a primary tumour. A post-mortem case treated with œstrogens for thirteen months. (× 300.)

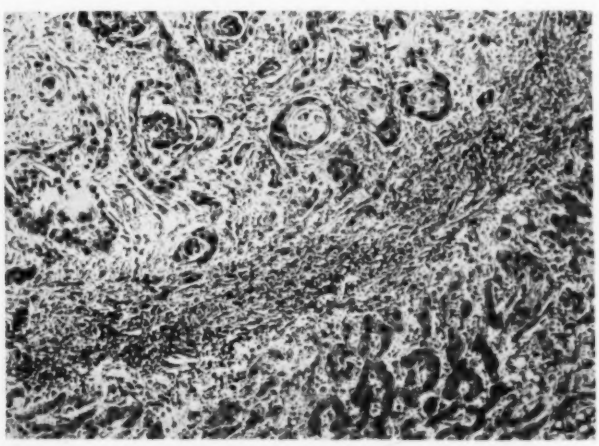

FIG. 489.—T. R. 4. Showing squamous metaplasia in secondary deposit in liver. (× 232.)

FIG. 490.—C. E. 2. Showing marked squamous metaplasia of the epithelium of the prostatic urethra. Œstrogen treatment for 16 months. (× 232.)

Œstrogen Effects on the Tumour Cells.—The first change is the appearance of small intracytoplasmic basal vacuoles which coalesce, forming a large swollen 'balloon' cell with the nucleus pushed to one side. These swollen 'balloon' or 'signet' cells are often desquamated and fill the alveolar lumina. The nucleus becomes condensed, hyperchromatic, and later pyknotic. More rarely there may be vacuole formation in the nucleus, which becomes hydropic and pale staining (*Figs.* 481–486). Later these swollen cells rupture, with dissolution of the normally sharp epithelial-stromal margin and diffusion of cell and alveolar contents into the stroma. This produces a pale-staining vacuolated stroma with finely fibrillar basophil strands (*Fig.* 487). The appearance is similar to the mucoid areas seen in 'mixed' tumours of salivary glands and probably has a similar cause. These changes may be followed by replacement fibrosis.

In one case a primary tumour and in another a liver metastasis showed squamous metaplasia after long œstrogen therapy (*Figs.* 488, 489). Synthetic and non-synthetic œstrogens produce an identical effect and this effect differs from the effects of

Table I.—SUMMARY OF FINDINGS

CASE	BIOPSY/ AUTOPSY	TUMOUR GRADES	HISTOLOGY		CLINICAL CHANGES			
			Œstrogen Response		*Local Malignancy*	*Clinical Response*	*Breast Response*	*Metastases*
			Tumour	Normal tissue				
Group I. Survival Period over 12 Months								
W. A. (alive 27 months)	Initial 3 weeks	H A	− +	NI NI	+ +	G	−	−
C. A. (died 17 months)	Initial 9 months 8 months	H A H	− − −	− NI NI	+ + +	G	±	+
W. B. (alive 14 months)	Initial 13 months	H H	− −	NI +	± +	G	+	+
W. B. (died 90 months) (I)	Initial 5 months 11 months 19 months 55 months	H H A A H	? ? + + −	NI NI + + +	+ + ± − ±	G	+	+
H. B. (alive 109 months)	Initial 1 week 17 months	A A A	+ + +	NI NI NI	+ + −	G	±	+
R. B. (alive 27 months)	Initial 17 months	A A	? +	NI NI	± −	F	+	−
P. B. (died 24 months) (I)	Initial 24 months	A A	− ?	NI NI	± ±	F	±	−
J. C. (died 29 months)	Initial 5 months 24 months	A A A	+ + −	NI NI NI	+ ± ±	F	+	+
W. C. (died 52 months)	Initial 45 months 7 months	A H A	− − −	− NI −	+ − ±	G	+	−
C. E. (alive 33 months)	Initial 16 months 6 months 4 months	A ? ? H	− ? ? −	NI + + +	+ + + +	G	+	−
H. E. (died 24 months)	Initial 24 months	H H	± −	NI NI	+ +	F	+	−
A. F. (alive 59 months)	Initial 22 months	A A	− −	NI NI	+ +	G	+	−
J. H. (died 30 months) (I)	Initial 7 months	A A	+ −	NI NI	+ +	G	+	−
G. H. (alive 22 months)	Initial 2 weeks 1 month	H H L	? ± +	NI NI NI	+ + +	D	±	−
A. H. (alive 34 months)	Initial 30 months	L H	− +	NI +	+ −	G	+	+
H. M. (alive 54 months)	Initial 17 months 28 months	H A A	− + −	NI NI NI	+ + ++	G	++ ++	−
C. M. (alive 30 months)	Initial 2 months	A A	− −	NI NI	+ +	G	±	−
T. R. (died 30 months)	Initial 30 months	A H	− ±	NI NI	+ +	G	+	−
B. R. (died 37 months)	Initial 37 months	A H	− −	NI ±	− ++	F	±	+
H. S. (alive 36 months)	Initial 2 weeks	A ?	− −	NI +	+ +	F	+	−
A. T. (alive 40 months)	Initial 11 months 17 months	A A A	+ + −	NI NI NI	+ − +	G	++	+
W. T. (died 44 months)	Initial 35 months 7 months	A H H	− − −	− NI +	+ ± +	G	+	−
W. W. (alive 71 months)	Initial 12 months	A H	− ?	− +	+ −	G	+	−

Table I.—SUMMARY OF FINDINGS (*continued*)

CASE	BIOPSY/ AUTOPSY	TUMOUR GRADE	HISTOLOGY		CLINICAL CHANGES			
			Œstrogen Response		*Local Malignancy*	*Clinical Response*	*Breast Response*	*Metastases*
			Tumour	Normal tissue				
Group II. Survival Period 1–12 Months								
J. J. (alive 4 months)	Initial	H	−	NI	+	N	−	+
	2½ months	(squamous carcinoma)	−	NI	+			
	1 month		−	NI	+			
F. J. (died 2 months)	Initial	A	?	NI	+	N	?	−
	2 months	A	±	NI	+			
C. K. (died 4 months)	Initial	H	±	NI	+	N	−	+
	4 months	H	−	NI	+			
W. L. (died 7 months)	Initial	A	+	+	+	G	+	+
	6 months	A	±	+	−			
	1 month	A	−	NI	−			
G. W. (died 12 months)	Initial	H	−	NI	+	D	−	−
	12 months	H	−	NI	+			
Group III. Survival Period up to 1 month								
C. C. (died 2 weeks)	Initial	A	−	NI	+	N	−	+
S. D. (died 2 weeks)	Initial	A	−	NI	+	N	−	+
	2 weeks	A	−	NI	+			
G. R. (died 1 month) (I)	Initial	H	−	+	+	N	−	+
	1 month	H	+	NI	+			
E. S. (died 2 weeks)	Initial	A	−	NI	+	N	−	+
	2 weeks	H	−	NI	+			
J. W. (died 3 weeks)	Initial	H	−	NI	+	N	−	+
	3 weeks	H	−	NI	+			

I = Died of intercurrent disease. L = Low. F = Fair.
H = High. NI = No information. D = Doubtful.
A = Average. G = Good. N = None.

Table II.—COMPARISON OF HISTOLOGICAL CHANGES AND CLINICAL STATE

	CLINICAL MALIGNANCY	GENERAL CLINICAL RESPONSE	BREAST RESPONSE	INITIAL METASTASES	TUMOUR GRADE		CHANGE OF GRADE	ŒSTROGEN RESPONSE		DEVELOPMENT OF ŒSTROGEN RESISTANCE
					Initial	Final		Tumour	Normal tissue	
Group 1: (23 cases surviving one year or more)	+ 22	Good, 16 Fair, 6 Poor, 1	+ 16 ± 6 − 1	+ 8 − 15	Low, 1 Average, 15 High, 7	Low, 1 Average, 11 High, 11	Better, 6 Worse, 11 Same, 6	+ 10 ± 6 − 7	+ 8 N.N.T.	17 Cases
Group 2: (5 cases surviving 1–12 months)	+ 5	Good, 1 Poor 1, None, 3	+ 1 N.I., 1 − 3	+ 3 − 2	Low, 0 Average, 2 High, 3	Low, 0 Average, 2 High, 3	Better, 1 Worse, 0 Same, 4	+ 1 ± 3 − 1	+ 1 N.N.T. 4	5 Cases
Group 3: (5 cases dying within 1 month)	+ 5	− None, 5 −	− 5	+ 5	Low, 0 Average, 3 High, 2	Low, 0 Average, 1 High, 4	Better, 0 Worse, 3 Same, 2	+ 1 ± 0 − 4	+ 1 N.N.T., 4	4 Cases

N.I. = No information. N.N.T. = No normal tissues.

radiotherapy or similar treatment in that cells at all stages of differentiation and in all grades appear to be equally sensitive.

Œstrogen Effects on Non-malignant Tissue.—The most striking change was a squamous metaplasia of transitional epithelium of the prostatic urethra extending into the prostatic ducts for a variable distance (*Fig.* 490). True keratinization was not seen. This effect remains prominent even when the tumour is no longer œstrogen-sensitive. In two cases there was active and irregular multifocal squamous metaplasia of such degree as to suggest the possibility of primary squamous carcinomata of urinary epithelium. It is impossible to say whether this was an œstrogen effect or co-incidental.

Œstrogens appear to have a much less marked effect on the epithelium of the "prostatic adenoma", sometimes causing cytoplasmic vacuolation and

producing a clear, almost structureless, cytoplasm, but no evidence of nuclear pyknosis or cell death.

The material did not allow a study of the effects on the prostate proper.

Findings.—The cases were divided into three groups depending on the survival period: Group I, over 12 months; Group II, 1–12 months; Group III, less than 1 month. The results are shown in *Tables I* and *II*. *Table III* shows the results when the cases are divided into four further groups, depending on the clinical findings on rectal examination.

DISCUSSION

In all but one case it was possible from the histological evidence to decide whether there had been previous œstrogen therapy. These œstrogen changes may appear within a very short time after beginning treatment—less than twenty-four hours in some cases (not in this series).

Histological evidence of continued œstrogen effects on the tumour was generally paralleled by clinical evidence of regression (*Table III*), but in no case were all the tumour cells destroyed. Even in

Table III.—PROSTATIC CARCINOMA—RESPONSE TO ŒSTROGENS

(Comparison of Rectal Findings with Œstrogen Response of Tumour)

RECTAL PALPATION OF PROSTATE	NUMBER OF CASES	SUSTAINED ŒSTROGEN RESPONSE OF TUMOUR		
		+	±	−
Improvement	6	4	1	1
Initial improvement, later relapse	4	0	2	2
No improvement	21	3	5	13
Deterioration	2	0	0	2

sections showing very severe degenerative changes in the greater part of the tumour, a few cells showing no sign of damage could always be found. These surviving cells were often, but not always, of dark-cell type.

After some time the tumour cells appear to lose their sensitivity to œstrogens and show no signs of cell damage even after very large doses have been given. This loss of œstrogen sensitivity was not restricted to any particular cell type or structure, and histologically the structure was as a rule similar to that of the original tumour, and œstrogen changes were still seen in the normal tissues. In some cases a tumour which had apparently become resistant showed marked œstrogen effects when the dosage was increased, so that one must distinguish between a relative and an absolute loss of sensitivity. It seems probable that the former represents the effects of inadequate dosage rather than a true biological change in the tumour. Ordinary histological methods do not show any change in character between the resistant and sensitive cells. Another possibility is that the development of œstrogen resistance is due to changes in the host rather than in the tumour. Further work on this problem is planned.

Table III shows a good correlation between the clinical evidence of regression in the prostate and the histological evidence of continued cell destruction, the only exceptions being two patients who died from extensive metastases.

A breast response, too, is as a rule associated with a good clinical response (16 out of 23 cases in Group I), but 1 case (W. A.) alive and well after twenty-seven months has never shown any breast changes.

There was no direct correlation between the grade of the tumour and the clinical course, but the final grade was generally worse than the initial grade.

Metastases were present when the patient was first seen in all but one case in Group III (this man died from an intercurrent disease), but in only 8 of 23 cases in Group I, so that, as might be expected, the presence of metastases tends to reduce the survival period, but there are exceptions to this, e.g., *Case* W. B., who had bone metastases when first seen and yet survived for nearly eight years, dying with coronary insufficiency.

In a few cases the primary tumour in the prostate remained small, soft, and histologically well-differentiated, but metastases were more anaplastic and rapidly growing.

SUMMARY AND CONCLUSIONS

Clinical regression of primary prostatic carcinoma after œstrogen therapy is associated with histological evidence of cell destruction in the prostate. In almost all cases the tumour cells, but not the normal tissues, eventually lose their sensitivity to the hormone. The reason for this is not known, but a relative loss due to inadequate dosage occurs in some cases. The resistant tumour cells have no specific histological characters, but are often of dark-cell type in solid trabeculæ. A most important point is that even in cases showing a very marked histological response to œstrogens there are always surviving tumour cells; thus it is unlikely that endocrine treatment alone can ever be expected to 'cure' prostatic cancer.

Grading is of little value in assessing prognosis or response to treatment, as œstrogen sensitivity of the tumour cells is independent of the degree of differentiation or anaplasia.

The presence of metastases when the patient is first seen tends to reduce the survival period.

A breast response to œstrogens is often associated with a good clinical response.

It is obvious that the optimum dosage of œstrogens has yet to be found, and this may well be higher than that generally used. Clinical records based on the subjective response, the behaviour of the primary growth and accessible metastases, and on the development of breast swelling and other side-effects, indicate that in many cases a period of a few days with doses ranging between 5 and 10 mg. stilbœstrol o.d. may be sufficient to produce an initial effect. In others, three to four weeks may elapse before any change is noted, and in some the condition appears entirely unresponsive. Repeated estimation of the serum

acid-phosphatase demonstrates a similar variability. Although an œstrogen response may often be observed in the tissues within a day or two of commencing therapy, a period of treatment lasting at least two to three weeks would seem desirable before any attempt is made at histological comparison. The use of other hormones, e.g., of pituitary origin, is being investigated in cases where the prostatic tumour has become œstrogen-resistant.

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BILATERAL CARCINOMA OF THE BREAST

BY A. J. M. REESE
DEPARTMENT OF PATHOLOGY, ST. GEORGE'S HOSPITAL MEDICAL SCHOOL, LONDON

"MALIGNANT primary epithelial neoplasia in the two breasts is rare." This view of Cheatle and Cutler (1931, a) is not shared by other authors. Bérard and Ballivet (1939) found 30 cases (4·8 per cent) of bilateral disease in 645 patients with breast carcinoma. In 9 cases there was evidence of spread from one side to the other via lymphatics; in 10 cases the growths were simultaneous; in 6 of the remaining 11, the first tumour was separated by less than 18 months from the second. Harrington (1946) studied 6559 cases treated by mastectomy in which 212 (3·2 per cent) had bilateral cancer and a further 62 (0·9 per cent) had tumours in both breasts simultaneously. Finney, Merkel, and Miller (1947) had 6 cases (2 per cent) in 298 patients with breast carcinoma, while Desaive (1949), examining material from 1259 cases of breast tumours, found 55 cases (4·4 per cent) with simultaneous bilateral cancer and 46 cases (3·5 per cent) in which a second primary occurred some time after the first. In addition he had 44 cases of cancer of one breast spreading to involve the other, and 15 cases of fibro-adenoma in one breast and cancer in the second.

Most surgeons are reluctant to admit that the second breast may frequently become the site of a primary carcinoma following the treatment of the first for this disease; it is generally maintained that bilateral involvement of the breasts results from dissemination of a single primary growth. Lenormant (1934) gave an elaborate description of possible pathways of spread from one breast to the other, and Hartmann and Guérin (1936) regarded bilateral breast cancer as most commonly the result of lymphatic metastasis. Moran (1930), in a review of the literature, concluded that whereas metastases in the opposite breast were relatively frequent, the incidence reaching 18 per cent in advanced cases (Handley, 1922), two primary growths were extremely rare. He pointed out that Schimmelbusch's disease, regarded by Cheatle as precancerous, was commonly bilateral, and it was strange that bilateral primary cancinoma was not therefore more frequent. He postulated some type of immunity given by one cancer to prevent further malignant change occurring. The most striking case of lymphatic spread is described by Teichmann (1932). A woman, aged 35, noticed a lump in her right breast. A year later she developed retraction of the nipple and at the same time a lump was found in the outer half of the left breast. She then had bilateral mastectomy. On the right side, the lump did not extend within 3 cm. of the right border of the sternum, but on sectioning the intervening subcutaneous tissues, all the lymphatic channels were stuffed with carcinoma.

Cheatle and Cutler (1931, b) regarded multicentric carcinoma of the breast as a very great rarity which usually affected only one gland. Caylor and Hunt (1929) described such a case. In 1927 a woman of 35 had a left mastectomy for 11 nodules of adenocarcinoma varying in size from 0·3 to 1 cm. Two years later the right breast was removed and 33 similar tumours were found, the largest 3 × 2 × 1 cm.

In any consideration of multiple carcinoma, it is important to examine the evidence advanced to prove the individuality of the tumours. Warren and Gates (1932) insisted on each tumour being distinct and presenting a definite picture of malignancy, the possibility of metastasis being excluded. Offergeld (1929) stressed that it was important to exclude retrograde lymphatic spread. Desaive (1949) had three criteria for the individuality of tumours: First, he mentioned difference in histological type, but explained that this might be unreliable and also that the converse did not exclude. Secondly, if both breasts contained cancer but no metastases occurred elsewhere, then it could be presumed that both tumours were primary. Lastly, if cancer appeared in the second breast some considerable time after the first had been removed, and if no metastases from the first were present, the second was then a primary growth. Cheatle and Cutler (1931, a) regarded the presence of epithelial neoplasia within the elastica as important in determining the primary nature of a growth. However, although the presence of intraduct carcinoma is a good demonstration that tumour is arising *de novo* in that place, the elastic around the ducts, though sometimes prominent, is often very inconspicuous and difficult to show by ordinary methods.

From 1938 to 1951, 504 patients were treated in St. George's Hospital for carcinoma of the breast.

Twenty (4 per cent) of these patients had bilateral growths and in 15 of them (*Cases* 1–15) there was clinical and histological evidence that both were distinct primary tumours. The remaining 5 (*Cases* 16–20) were advanced cases in which the possibility of spread from one breast to the other could not be excluded. Following the description of each case below, evidence, if any, for the individuality of the tumours has been put forward in its place. *Figs.* 491–494 illustrate histological differences in the first and second tumours of two of the cases, while *Figs.* 495 and 496 show both the tumours of a third case arising in intraduct carcinoma.

CASE REPORTS

Case 1.—D. R., aged 47, had a right radical mastectomy on Feb. 4, 1936, for a lump in the breast which had been present for eight months. Microscopically it was a spheroidal-cell carcinoma in dense stroma and surrounded by chronic mastitis with intraduct carcinoma. Nine years later, on April 7, 1945, a radical mastectomy was performed for a tumour in the upper, outer quadrant of the left breast. Microscopically this was a similar tumour, again with intraduct carcinoma. She received post-operative deep X-ray therapy (D.X-R.T.) and was well on Sept. 18, 1950, when last seen.

This patient had two similar growths each arising in an intraduct carcinoma with an interval of nine years between them. She was well five years following her second operation.

Case 2.—M. C., aged 65, had a radical mastectomy at another hospital on Sept. 11, 1941, for a lump in the right breast. Microscopically the growth was a clear-celled carcinoma with an alveolar arrangement in a very dense stroma containing cholesterol clefts. The glands were not invaded. Eight and a half years later, on March 16, 1950, a left local mastectomy was performed for a lump behind the nipple. Microscopically this was a papillary carcinoma with a dense fibrous stroma. She was well when last seen on Aug. 21, 1950.

The first tumour had not recurred elsewhere and the second growth eight and a half years later was very different from it in microscopical appearance.

Case 3.—W. M., aged 34, was treated by right radical mastectomy on July 21, 1942, for a lump in the upper outer quadrant of the breast which had been present for two years. Microscopically it was a spheroidal-cell carcinoma growing in broad trabeculæ in a dense stroma. The cells showed occasional attempts at acinar formation. The axillary glands were not invaded. She had post-operative D.X-R.T. and remained well for almost nine years until June 21, 1951, when a lump in the upper outer quadrant of the left breast was treated by radical mastectomy. Microscopically this was a spheroidal-cell carcinoma in a dense stroma, surrounded by chronic mastitis with intraduct carcinoma. Two of five axillary glands examined were invaded.

There had been no recurrence of the first growth and nine years later the second developed in the opposite breast, arising from intraduct carcinoma.

Case 4.—M. F., aged 46, was admitted in 1931 with two lumps in the right breast; one had been present for seventeen years and the other for six months. A radical mastectomy was performed, and on microscopical examination the first tumour was an intracanalicular fibro-adenoma and the second a papillary carcinoma with large areas of necrosis. There was no recurrence of these tumours and eight years later, on June 4, 1939, she was re-admitted for a lump in the upper outer quadrant of the left breast which had been present for a year. A radical mastectomy was performed. Microscopically this was a spheroidal-cell carcinoma producing mucin and growing in a dense stroma. A secondary deposit in an axillary gland showed acinar formation which was absent in the primary. She was last seen with no sign of recurrence on Nov. 15, 1944, since when it has not been possible to trace her.

In addition to the fibro-adenoma, this patient had two morphologically distinct carcinomata appearing with an interval of eight years between them.

Case 5.—M. H., aged 52, had a left radical mastectomy on May 11, 1943, followed by D.X-R.T., for a lump above the nipple which had been present for four months.

FIG. 491.—*Case* 6, left breast. A columnar-cell papillary carcinoma which is also seen growing in narrow trabeculæ in a fibrous stroma. (H. and E.) (× 36.)

This was an adenocarcinoma growing both in rounded clumps and narrow trabeculæ in a fibrous stroma with intraduct carcinoma. She had no recurrence of this, but seven and a half years later, on Nov. 16, 1950, a radical mastectomy was performed for a lump in the right breast which microscopically was a large clear spheroidal-cell carcinoma undergoing extensive necrosis and growing in a dense calcified stroma. The axillary glands were not involved.

The first carcinoma showed no sign of recurrence after treatment. The second, occurring after an interval of seven and a half years, differed from the first in microscopical appearance.

Case 6.—B. B., aged 76, was operated upon at another hospital in November, 1944, for the local removal of a lump in the upper part of the left breast. Microscopically this was a large clear columnar-cell papillary carcinoma which was also growing in narrow trabeculæ of large spheroidal cells in a very fine stroma (*Fig.* 491). She received D.X-R.T. and remained well for six years, but on Jan. 18, 1951, a local mastectomy was performed on the right breast for a lump beneath the nipple. This proved to be a cribriform adenocarcinoma, with areas of necrosis, growing in a dense stroma (*Fig.* 492).

No metastases were present from the first tumour, and the second, appearing six years later, was very different in microscopical structure.

Case 7.—M. P., aged 39, had a radical mastectomy on May 10, 1946, followed by D.X-R.T., for a tumour in

the lower outer quadrant of the right breast. Microscopically this was a spheroidal-cell carcinoma surrounded by cystic mastitis with intraduct carcinoma. There was no recurrence of this tumour, but some four years later, on Sept. 25, 1950, she reported a lump in the upper outer

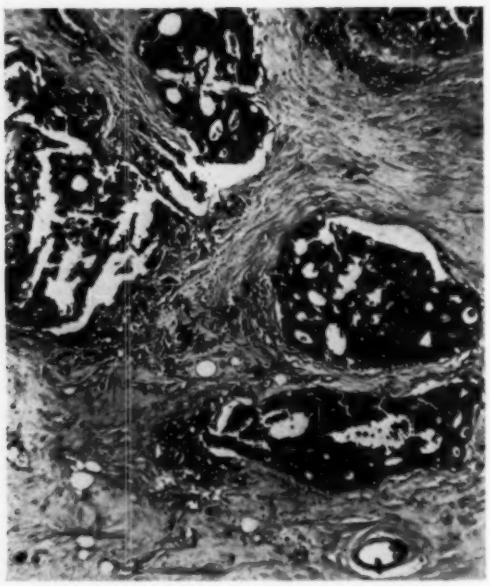

FIG. 492.—Case 6, right breast. A cribriform adenocarcinoma in a dense stroma. (H. and E.) (× 40.)

quadrant of the left breast. Unfortunately a biopsy was not taken and she was treated by D.X-R.T. alone. When she was last seen on Oct. 23, 1950, the lump had regressed in size.

The first tumour had apparently been cured and the second had arisen in the upper outer quadrant of the opposite breast four years later.

Case 8.—B. B., aged 48, had a right local mastectomy in another hospital in September, 1939, for a spheroidal-cell carcinoma growing in an area of cystic mastitis but without intraduct carcinoma. Four years later, on Sept. 22, 1943, she had a left radical mastectomy for a lump which had been present for one month. A section of this was not available, but it was reported as " scirrhous carcinoma Grade I; inflammatory changes only in glands ". On Oct. 2, 1944, a lump was removed from the right axillary tail which showed spheroidal-cell tumour accompanied by cribriform intraduct carcinoma. She received post-operative D.X-R.T. and was well on June 26, 1950.

The patient had a second primary in the opposite breast four years after the first had been removed. A year later a third primary tumour arising in intraduct carcinoma was present in the remaining axillary tail of the first breast.

Case 9.—I. T., aged 44, had a right radical mastectomy on Jan. 23, 1945, for a tumour of the inner half of the breast which had been present for eighteen months. Microscopically this was a mucoid carcinoma, the cells appearing in small clumps with an acinar arrangement. She received D.X-R.T. and remained well for five years, until a left local mastectomy was performed on May 16, 1950, for a tumour of similar histological appearance but growing in larger clumps with more marked acinar formation. The glands were not involved. She was well when seen last on Oct. 24, 1950.

In this case both tumours were similar histologically, but they arose at an interval of five years and there were no metastases from the first.

Case 10.—E. B., aged 35, was subjected in 1935 to a radical mastectomy for a lump in the right breast which she had noticed for two weeks. Microscopically it was an extremely necrotic carcinoma growing in large clumps in a very fine stroma. The glands in the axilla were not involved. Three years later, on May 5, 1938, a left radical mastectomy was performed for a lump in the upper inner quadrant of the breast. Microscopically this was a cribriform adenocarcinoma in a dense stroma. The glands were not involved. She had post-operative radium treatment but died on March 9, 1940, with pulmonary metastases. There was no post-mortem examination.

These two tumours, occurring at an interval of three years, showed very different microscopical appearances.

Case 11.—G. S., aged 60, had a right radical mastectomy at another hospital in 1943. The tumour was a papillary carcinoma, the fronds being covered by layers of cells with cribriform appearance (*Fig.* 493). Some intraduct carcinoma was present and the axillary glands were free from growth. Three years later, on March 15, 1946, a left radical mastectomy was performed for a tumour above the nipple. Microscopically this was a spheroidal-cell carcinoma with a slight attempt at acinar formation. There was chronic mastitis with epitheliosis surrounding the tumour (*Fig.* 494). The glands were not involved. She received D.X-R.T. and there was no sign of recurrence of either cancer on Nov. 9, 1950.

This patient had two morphologically distinct carcinomata at an interval of three years and has survived the second four years without sign of recurrence.

Case 12.—E. B., aged 49, had a left radical mastectomy on March 6, 1945, for a tumour which on microscopical examination was a cellular spheroidal-cell carcinoma surrounded by chronic mastitis and intraduct carcinoma. She received D.X-R.T. and remained well for three years until April 25, 1948, when she noticed a small lump in the right breast. This was locally excised and proved to be a large, clear, spheroidal-cell carcinoma surrounded by chronic mastitis and intraduct carcinoma. Despite this, the patient refused a second mastectomy and received D.X-R.T. She was seen last on Nov. 1, 1950, with a mass in the right breast.

These two tumours, occurring at an interval of three years, were histologically distinct and both were arising from intraduct carcinoma.

Case 13.—D. R., aged 52, had a lump in the upper inner quadrant of the left breast for four months which was treated on May 28, 1945, by radical mastectomy followed by D.X-R.T. Microscopically this was a polygonal-cell carcinoma with broad trabeculæ in a fibrous stroma. It was surrounded by an area of chronic mastitis, but there was no intraduct carcinoma. On Jan. 15, 1948, almost three years after the first operation, a right local mastectomy was performed for a lump in the upper outer quadrant. Microscopically this was an area of chronic mastitis with intraduct carcinoma. After a further two years, on April 8, 1950, the glands in the right axilla were excised and contained spheroidal-cell carcinoma. When last seen, on Oct. 30, 1950, there was a plaque of growth 5 × 3 cm. in the right axilla.

This patient had two cancers with three years interval between them. The second began as an intraduct carcinoma which later spread to the axillary glands.

Case 14.—A. C., aged 46, had a left radical mastectomy on Sept. 29, 1942, for a lump in the upper outer quadrant. Microscopically this was a spheroidal-cell carcinoma growing in an area of chronic mastitis and intraduct carcinoma. The axillary glands were not involved. On Aug. 5, 1944, after an interval of two years, a right radical mastectomy was performed followed by D.X-R.T. for a tumour in the right axillary tail which was a large clear spheroidal-cell carcinoma in a dense stroma amidst

chronic mastitis. The axillary glands were invaded. No sign of recurrence was seen on her last attendance on Nov. 4, 1950.

FIG. 493.—*Case* 11, right breast. A papillary carcinoma, the fronds covered by layers of cells with a cribriform appearance. (H. and E.) (× 28.)

FIG. 495.—*Case* 15, right breast. A spheroidal-cell tumour with cribriform intraduct carcinoma. (H. and E.) (× 40.)

This patient had two morphologically different cancers two years apart. She was well six years after the second operation.

Case 15.—M. I. had a radical mastectomy on Oct. 12, 1949, followed by D.X-R.T., for a tumour in the upper outer quadrant of the right breast which had been present for six months. Microscopically this was a spheroidal-cell tumour accompanied by cribriform intraduct carcinoma undergoing necrosis (*Fig.* 495). The axillary glands were free of growth. The following year, on Oct. 11, 1950, a second radical mastectomy was performed for two lumps in the left breast. Microscopically these were similar growths, also with intraduct carcinoma (*Fig.* 496).

FIG. 494.—*Case* 11, left breast. A spheroidal-cell carcinoma with chronic mastitis and epitheliosis. (H. and E.) (× 40.)

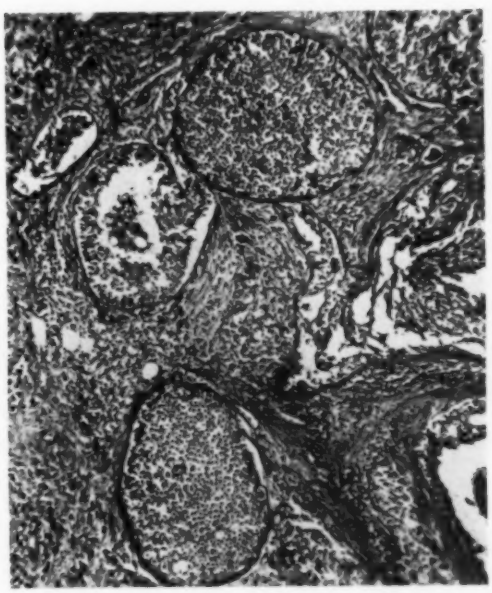

FIG. 496.—*Case* 15, left breast. A similar growth to *Fig.* 495, also with intraduct carcinoma. (H. and E.) (× 36.)

The growths in the two breasts, although separated by only about eighteen months, were each seen arising from intraduct carcinoma.

Case 16.—E. L., aged 71, had a radical mastectomy on Oct. 15, 1937, for a lump in the right breast which had been present for ten months. Microscopically it was a spheroidal-cell carcinoma in a very dense stroma. A gland was invaded. The next year, on July 12, 1938, she had a second radical mastectomy for a lump in the upper outer quadrant of the left breast which had a similar histological appearance. The glands were not

invaded. She died on Jan. 28, 1940. There was no post-mortem examination.

Case 17.—R. W., aged 62, presented on April 24, 1950, with the right nipple replaced by a fungating mass and with a lump in the upper inner quadrant of the left breast with retraction of the nipple. Biopsies were not performed and she was treated with D.X-R.T. She died on July 4, 1950, with metastases in the spine. Post-mortem examination was not made.

Case 18.—E. J., aged 70, presented on July 19, 1942, with a lump beneath the right nipple and another in the upper outer quadrant of the left breast. She had noticed the former tumour for eighteen months. Glands were palpable in both axillæ. A right local mastectomy was performed and microscopically the tumour was a small spheroidal-cell carcinoma in a dense stroma. It was invading the skin. No biopsy of the left breast was taken. She was given D.X-R.T. and when seen last on Oct. 29, 1946, had multiple metastases in bone. There was no subsequent trace of her.

Case 19.—H. H., aged 68, presented on Oct. 31, 1949, with lumps in both breasts and palpable glands in both axillæ. She had noticed the lump in the right breast for twelve months and the lump in the left breast for three months. Biopsies were not taken. She was treated with D.X-R.T. and attended last on Aug. 21, 1950.

Case 20.—E. B., aged 58, had a right radical mastectomy for cancer in another hospital on July 2, 1943, followed by D.X-R.T. No histological material was available for study. On Dec. 19, 1944, there was a mass of glands in the right supraclavicular fossa and a large tender lump in the left breast, with glands in the axilla. On June 8, 1945, a left local mastectomy was performed. Microscopically there was a large clear spheroidal-cell carcinoma in a fine stroma surrounded by cystic mastitis. She received more D.X-R.T., but died on Nov. 12, 1946. Post-mortem examination was not made.

DISCUSSION

Despite the extreme rarity of multicentric cancer and the frequency with which bilateral tumours have in the past been ascribed to metastasis, there is strong evidence that in *Cases* 1–15 of the present series the second growth is a primary carcinoma. In 7 of the cases (*Cases* 2, 4, 5, 6, 10, 11, and 14) the growths were morphologically very different, and in a further 5 (*Cases* 1, 3, 12, 13, and 15) the second tumour was clearly seen arising from intraduct carcinoma. In the remaining 3 cases, as in most of the others, there is clinical evidence in favour of two primary tumours. The first tumour was in each case removed without local or distant metastases several years before the appearance of the second growth. Removal of the second breast often resulted in a 5-years' 'cure'. If the second tumour were a metastasis of the first, it is strange that secondaries had not occurred elsewhere.

In order to discover whether a particular morphological type of tumour is frequently associated with bilateral carcinoma, the twenty-nine separate growths examined in *Cases* 1–15 were compared with the hundred most recent unilateral breast carcinomata seen in the department. The results given in *Table I* show no marked difference in the frequency of morphological types in bilateral and unilateral cancers.

It is of more than academic interest to determine whether the development of malignant change is the sequel to a local abnormality or growth disturbance, or whether it is the result of some systemic effect, presumably a humoral mechanism, acting on the tissue as a whole. The frequency of cases showing individual and successive primary tumours in the two breasts observed in this study supports the latter hypothesis. There is evidence that failure to reproduce and to lactate predisposes to mammary cancer (Willis, 1948). Histories of pregnancy and suckling were unfortunately not available in the cases described, but it seems reasonable to postulate that an endocrine or other cause leading to a first cancer may continue to act to initiate a second after the first has been eradicated.

SUMMARY AND CONCLUSIONS

Out of the 504 cases of mammary cancer treated in St. George's Hospital from 1938 to 1951, 20 were bilateral.

The clinical and microscopical features of these cases of bilateral carcinoma are described; in at least 15 of them there is evidence that both tumours were primary.

The conclusion is drawn that bilateral breast carcinoma is more often due to two primary tumours than to dissemination of a single growth.

Table I.—Morphological Types of Cancer of Breast

	Spheroidal Cell	Adenocarcinoma		Diffuse Polymorphic	Intraduct Only	Tumours Showing	
		Alveolar	Papillary			Intraduct Carcinoma	Mucoid Change
29 tumours from *Cases* 1–15 of bilateral carcinoma	19 (65·5 per cent)	5 (17 per cent)	4 (14 per cent)	0	1 (3·5 per cent)	14 (48 per cent)	3 (10·5 per cent)
100 tumours from cases of unilateral breast carcinoma	62	25	6	5	2	59	7

My thanks are due to the surgeons on the staff of St. George's Hospital for permission to use their clinical notes, especially to Mr. Victor Riddell, who supplied 13 out of the 20 cases. I am also indebted to the pathologists from other hospitals who sent me the missing histological material, and to Professor T. Crawford for his advice and encouragement.

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LINDAU'S DISEASE

IN A SOUTH AFRICAN FAMILY

BY ALLAN V. BIRD AND ROWLAND A. KRYNAUW

FROM THE DEPARTMENT OF NEURO-SURGERY, JOHANNESBURG GENERAL HOSPITAL

THE part of heredity is difficult to establish in the aetiology of most tumours. In some, however, it is undeniable. Hæmangioblastoma of the cerebellum is one such tumour.

Lindau described a family with cerebellar hæmangioblastomata in six members spread over three generations (1931). These tumours, besides their interesting familial incidence, have this additional feature: they are frequently associated with tumours elsewhere in the body—in the retina, pancreas, kidneys, spleen, spinal cord. The association of cystic tumour of the cerebellum with cysts of the kidney and pancreas was first described by Pye-Smith (1884), but the condition has become linked with Lindau's name because of his contributions towards its elucidation and better understanding (1926).

Lindau's disease has been defined by Greenfield and Carmichael (1938) as hæmangioblastoma of the cerebellum associated with: (1) similar changes in the retina; or (2) benign tumours in the kidney, adrenals, and pancreas; or (3) a cystic condition of the kidneys and pancreas.

Vascular tumours are rare in the brain—2 per cent according to Cushing and Bailey's figure (1928); 5 per cent according to Dandy (1928). Of 100 consecutive tumours of the brain and spinal cord examined in this laboratory, 7 were diagnosed as being of the angiomatous group; 4 were cerebellar, 2 from the spinal cord, and 1 from the occipital pole. No reference in the literature was found to supratentorial tumours as part of Lindau's disease; angiomas in general are rare in this situation (Barnard and Walshe, 1931).

Such case-histories of Lindau's disease as are available have clearly demonstrated the familial nature of the condition and that it is not sex-limited. There are reports of several members of two or three generations being afflicted with the condition.

With improving neurosurgical technique, tumours of the posterior fossa do not carry the same hazards as they did fifteen or twenty years ago. Craig, Wagener, and Kernohan (1941) have reported three of four suffering from Lindau's disease surviving operation.

In the family to be described, five siblings underwent operation for Lindau's disease, all except one surviving. This case, as will be described below, presented unusual difficulties and was complicated by a diabetic state.

CASE REPORTS

The family was of Afrikaans origin—whites of mainly Dutch ancestry—and was located in an isolated part of the Northern Transvaal. The parents of our patients died many years ago. The father married twice and certain of the offspring of each marriage were afflicted with Lindau's disease, clearly establishing him as the transmitter of the condition. There was some disagreement amongst his children as to his mode of death, some saying that he died at 62 of a stroke, others contending that he was blind in one eye, had a tremor similar to their own, and died with severe headache and vomiting. It is possible, then, that he, too, had Lindau's disease.

Case 1.—The first patient of the family to seek advice was H. N. (II_{11} on family tree) aged 18, who was referred to the Neurosurgical Department of the Johannesburg General Hospital on April 21, 1943.

For the previous eighteen months he had suffered from occipital headaches, paroxysmal in character, lasting up to half an hour before gradually subsiding, and occurring two to three times per day. An unusual feature was that during attacks the right side of his face and tongue felt numb.

Three weeks prior to his admission his vision suddenly became impaired and deteriorated so rapidly that when he was examined he was able to distinguish light and dark only.

The examination revealed a high degree of papilloedema and, already, signs of consecutive optic atrophy. There was a slight external strabismus of the right eye, but external ocular movements were normal and there was no evidence of nystagmus. Facial sensation was slightly impaired on the right side and the tongue was protruded to the right. Vague signs suggestive of a cerebellar lesion were noted on the left side. In view of his extremely bad general condition a catheter was inserted through a left parietal bur hole into the ventricle and continuous ventricular drainage established. Within a week his condition had improved sufficiently to justify ventriculography.

This revealed grossly dilated lateral and third ventricles, without shift. The proximal part of the aqueduct was visualized, slightly dilated and kinked. The fourth

ventricle was not outlined. An obstruction in the region of the fourth ventricle as from a cerebellar tumour was diagnosed.

Accordingly, on the same day, the posterior fossa was explored through a horseshoe-shaped incision. The cerebellar tonsils were found to be jammed down through the foramen magnum as far as the second cervical vertebra. The cerebellum itself was grossly ballooned and the vermis widened. A large cyst was palpated, undermining the vermis but extending laterally in both directions, mainly to the right. A brain needle was inserted and some 30 c.c. of yellow fluid withdrawn, causing the cerebellum to collapse. The cyst was decapped widely and found to contain a cherry-red

Mr. Krynauw opened her posterior fossa and dealt with a typical cystic hæmangioblastoma. She made an uncomplicated recovery. She was examined in June, 1950, and had a visual acuity of 6/6 in each eye and no abnormal neurological signs could be elicited. In fact, but for the scar across her occiput, the observer would have difficulty in believing that she ever had any neurological lesion.

Case 3.—The third case (II_{10}), A. N., aged 21, was seen on July 21, 1945. His history was acute, being of only one month's duration. He complained of severe occipital headaches with nausea and vomiting. His vision in the left eye had been impaired for some years,

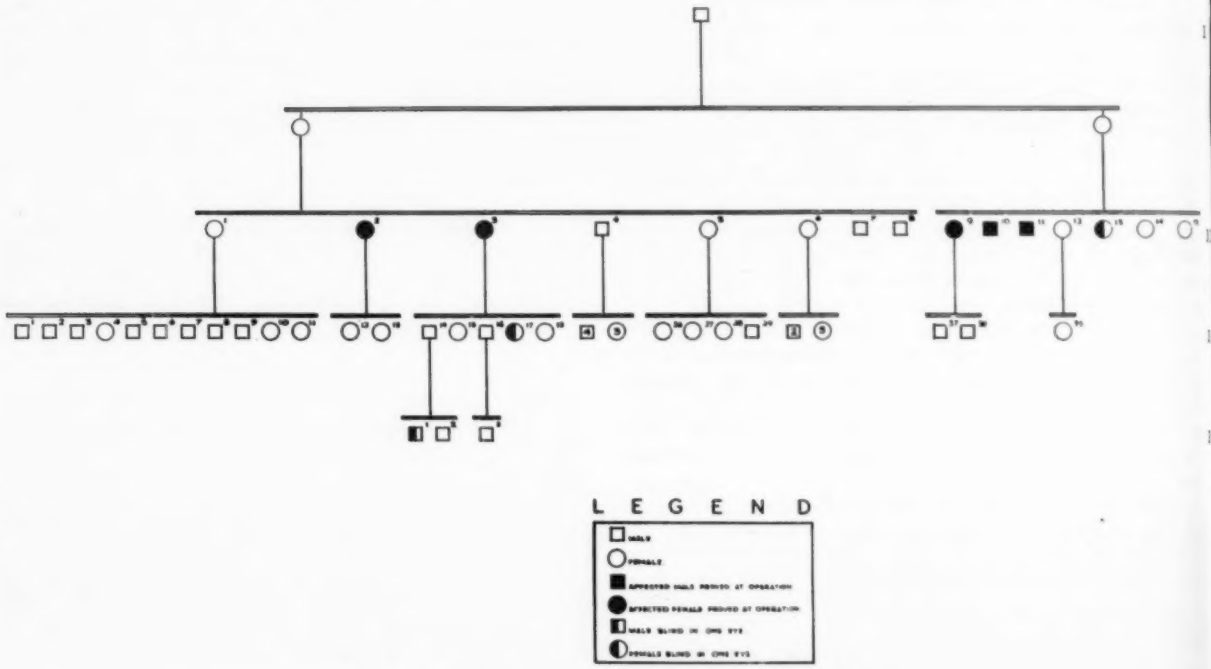

FIG. 497.—Lindau's disease : pedigree of a South African family.

nubbin about 1·5 cm. in diameter lying medially and superiorly. This was completely removed, but only with difficulty owing to the extreme vascularity of the lesion and its situation high up under the tentorium.

Pathological examination of the mural nubbin revealed the structure of a hæmangioblastoma.

After a stormy period immediately following operation, the patient made slow but satisfactory progress, being discharged from hospital some three months after operation. He was seen recently, five years after removal of his tumour. Apart from his blindness, he was very well, earning a living making baskets in an institute for the blind. He had no abnormal physical signs.

Case 2.—The second of the family to be seen was H. v R., a sister of the first patient (II_9 on the family tree). She consulted Dr. Geerling on Feb. 15, 1945, about headaches of five months' duration associated latterly with vomiting and a sensation of her head being pulled backward.

Examination revealed clumsiness and weakness of the left arm and leg, nystagmus, and a staggering gait, with stumbling to both sides but more markedly to the left. Three dioptres of papillœdema were noted.

In view of the history of hæmangioblastoma of the cerebellum in her brother, Lindau's disease was diagnosed.

but the right eye had deteriorated rapidly in the previous month. Titubation had been present for a similar period.

Examination revealed an angioma of the retina in the right eye, the vision in which was nil. The left eye showed 2 dioptres of papillœdema ; slight nystagmus on looking to the left was observed. Power was considered within normal limits. Slight cerebellar signs were noted on the left side, dysmetria, intention tremor, asynergia, but rapidly alternating movements were well executed. Left-sided Babinski reflex was present.

The posterior fossa was opened by Mr. Krynauw through a horseshoe-shaped incision. A large cyst occupying the greater part of the left cerebellar hemisphere was removed. In the process of decapping the cyst a mural nubbin was removed. Histological examination of this piece of tissue revealed the structure of a hæmangioblastoma (*see under* ' Pathology ').

The patient recovered rapidly from the operation and was last seen recently some five years after his operation, working as a farm foreman on a large estate in a subtropical part of South Africa. Apart from his right eye no signs of neurological abnormality could be found.

Case 4.—The fourth case (II_2), S. N., number one on the family tree, was a step-sister of the three patients so far described. In 1944 her right eye was removed for retinal angioma. The following year vision in the

remaining eye began to fail. In December, 1945, she was referred to us, suffering from periodic attacks of severe occipital headaches with temporary mental confusion and vomiting.

She was found on examination to have a staggering gait, intention tremor, dysmetria, and nystagmus. A diffuse papillœdema of 2 dioptres associated with signs of consecutive optic atrophy was present, vision being limited to perception of light only.

She underwent operation in January, 1946. Mr. Krynauw stabilized her intracerebral pressures with an indwelling ventricular catheter for one week. A large cystic hæmangioblastoma, together with a mural nubbin, was removed from the left cerebellar hemisphere.

This patient was seen again recently and, apart from her lack of vision, was very well. She was almost completely blind, although she stated that she sometimes saw spots of light and flashes even now. Ophthalmoscopic examination showed her disks to be a parchment-like grey colour with blurred edges and narrowed vessels.

As has been pointed out above, the four cases described were visited recently to check their progress. The opportunity was taken of examining some of their relatives. A girl of 17 (II_{13}), J. N., was seen who had recently had an eye removed for angioma of the retina. She had no signs to suggest intracerebellar neoplasm, but she will be examined from time to time as these may yet develop.

Case 5.—A sister (II_3) of S. N., described above, was found to have gradually lost the sight in one eye two years previously She had periodic attacks of severe headache with vomiting and pains down the right side of her body. Sugar and acetone had been found in her urine and diabetes diagnosed. She proved to be most difficult to

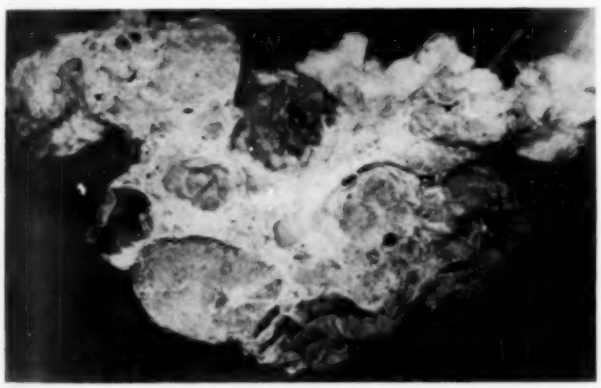

FIG. 498.—Pancreas from II_3 (*Case* 5), showing extensive cystic degeneration.

control with insulin. Vision in the left eye had begun to fail in recent months.

She was found on examination to walk on a wide base, staggering to the right and left. The right eye was blind, with a fixed pupil; a cataract prevented examination of the fundus. Vision in the left eye was 6/36 and there was loss of vision in the lower nasal fields. A low degree of papillœdema was present. There was no nystagmus. Her limbs were hypotonic with weak reflexes. Plantar responses were flexor. A slight degree of dysdiadochokinesis was present in the left hand, but otherwise fine finger movements were carried out neatly and skilfully. A cystic mass was palpated in her epigastrium.

Mr. K. Lewer Allen operated on July 1, 1950. The case was complicated by her intractable diabetic state. After a complete amputation of one cerebellar hemisphere containing a large tumour, an unsuspected second hæmangioblastoma was discovered in the remaining hemisphere and this, too, was removed.

She made good progress for the first five days following this extensive procedure and then succumbed to a secondary hæmorrhage into the posterior fossa.

At autopsy, carried out by Dr. B. F. P. Becker, her pancreas was found to be entirely replaced by cystic tissue (*Fig.* 498). Microscopical examination revealed disappearance of the islets of Langerhans. An angioma was found in the spleen, but the remaining organs were

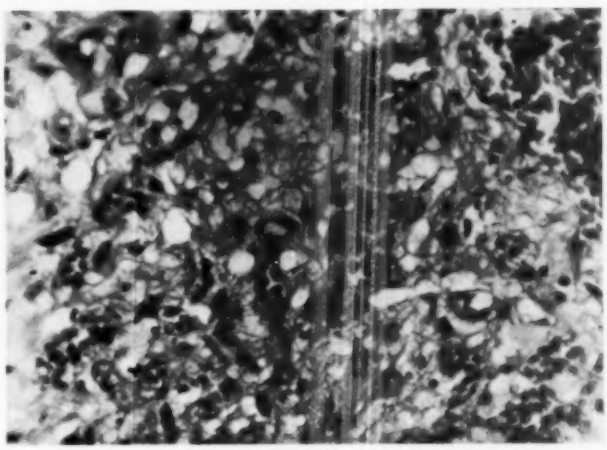

FIG. 499.—Detail of the structure of part of the tumour removed from II_3 (*Case* 5).

normal. These findings resembled those described by Davison, Brock, and Dyke (1936) in their case.

Finally it is of interest that a daughter (III_{17}), aged 20, of this patient, A. B., is blind in one eye, as is a grandson aged 2 years (IV_1). Each has a lens opacity which prevents further examination. It is possible that each has an angioma of the retina which has caused detachment and secondary cataract.

Pathology.—Unlike the tumours of the four siblings, those from A. B. (II_3) were not markedly cystic but were mainly cellular in structure (*Fig.* 499). No capsule was present.

The tumour structure varied markedly from place to place, showing gradations varying from clumps of adult type of vessel to aggregation of capillary spaces lined with only one layer of cells to masses of endothelial cells with only occasional blood-spaces. All these findings in one tumour tend to make one doubt the value of meticulous classification of the angioma group into multiple subdivisions, as has been attempted by some workers.

Sections stained with hæmatoxylin and eosin revealed the presence of isolated foam cells. Frozen section stained with Scharlach R showed these cells to contain bright red-staining lipid, a finding in keeping with the reports of Sargent and Greenfield (1929), who were surprised at the number of fat-containing cells in some of their angiomatous tumours.

Sections stained with van Gieson's iron-hæmatoxylin method demonstrated that just as the arrangement of endothelial cells varied in different parts, so, too, did the amount of collagenous connective tissue, being indiscernible in certain areas and present in thick branching bands in others.

Occasional giant cells were present, especially in areas where the endothelial cells lay in clumps. The latter cells varied considerably in morphology, tending to be rounded or ovoid in places, with well-filled cytoplasm. Elsewhere they presented almost a 'signet-ring'

appearance, the cytoplasm being attenuated to form the boundary of a capillary space.

Sections from the mural nubbin of A. N. (II_{10}), whose tumour was mainly cystic, showed little proliferation of endothelial cells but rather a predominance of connective-tissue stroma (*Fig.* 500). Again, there was no evidence

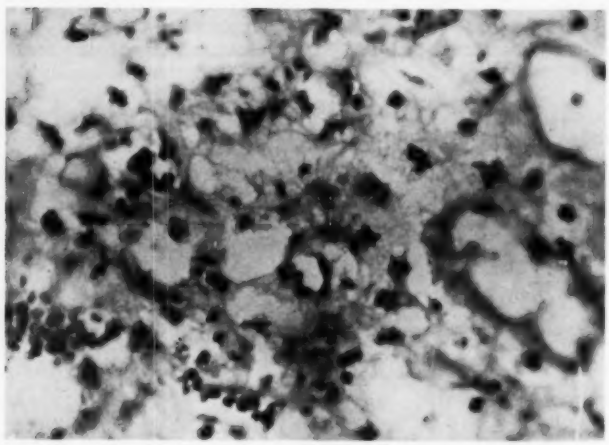

FIG. 500.—Portion of the tumours removed from II_{10} (*Case* 3).

of capsule between tumour and cerebellar tissue, except a slight aggregation of glial fibres.

Certain blood-vessels close to, but not forming part of, the tumour showed extensive proliferation of endothelial lining. Elsewhere in the cerebellum the blood-vessels were of normal appearance. Unfortunately pathological material from the remaining three cases was not available for special study.

DISCUSSION

This is the first family in South Africa to be described as suffering from Lindau's disease, although one of us (R. K.) has seen sporadic cases in which symptoms and findings at operation suggested this diagnosis.

The family is interesting genetically. The family tree, limited as it is, is sufficient to establish that the mode of transmission is as an autosomal dominant (Crew, 1947). Clearly the father (I) of our patients was the carrier of the affected genes, having transmitted them through his first and second wives. If we are correct in our assumption that this family shows autosomal dominance, then the father must have suffered from some form of the disease, a point only suspected from the clinical history. Of his fifteen offspring, six are known to suffer from the disease, one died at infancy. Had this child been affected the total number of those afflicted would approximate the expected 50 per cent of this type of transmission. In the third generation the only members affected are offspring of affecteds, and no normals have produced children with the affliction except the father of IV_1, who may yet develop the condition. It would appear that the family is showing the phenomenon of anticipation; I, if he was affected, did not show symptoms of the condition until his declining years—he died at 62. In the second generation the average age at the time of operation was 30 years, while in the third generation a child of 2 has shown signs of the affliction. Gates (1946) attributes the multiplicity of lesions of the syndrome to genes of polyphanic manifestation. It is regretted that more details of the ancestry of the family were not obtainable. The surviving members live in a backward part of the country and are singularly uninformed as to their forebears. It is, however, fairly certain that the first and second wives of I were not consanguineous.

Garrod (1902) was the first to demonstrate that the genetic causes of certain hereditary conditions could be detected biochemically. In the family described above it is possible that some inborn biochemical lack might be responsible for the transmission of the affliction. As our knowledge of this aspect of the problem increases, conceivably physical prophylactic measures will suggest themselves. Herein lies the best hope of controlling hereditary diseases, for as Penrose (1950) has pointed out: "in the present state of genetical knowledge, the prospects of making any appreciable change in the genetical composition of the population by preventive eugenics are remote". In Canada the Dominion Government is sponsoring a project to study and attempt to control biochemically a family afflicted with Leber's hereditary optic atrophy (Bird and McEachern, 1949).

For the present, neurosurgical technique has so improved as to make the surgical treatment of the intracranial manifestations of Lindau's disease a relatively simple and safe procedure.

We feel that a pre-operative period of five to seven days, during which the intracranial pressure mechanisms are re-adjusted by means of regulated indwelling intraventricular catheterization, is an important contributory factor. At operation, apart from dealing with the mural nubbin or focal zone of pathology, it is our practice, when decapping, to do a wide excision of all overlying and adjacent thinned-out cerebellar tissue, even if this means virtual amputation of an entire hemisphere and the region of the vermis.

SUMMARY

A South African family with Lindau's disease is described. Five members underwent operation and a sixth has had an eye removed for angioma of the retina. Two further siblings are blind in one eye at an early age. Genetic, pathological, and neurosurgical aspects are considered.

We wish to thank Dr. B. J. P. Becker for his assistance and advice, and for putting one of his laboratories at our disposal.

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ACUTE PHLEGMONOUS CÆCITIS

BY R. E. B. TAGART
ADDENBROOKE'S HOSPITAL, CAMBRIDGE

FREDERICK CHRISTOPHER (1936) has drawn attention to four morbid conditions which, though " not often seen in the average surgical practice . . . stand out as a constant threat to all who enter the peritoneal cavity expecting to find pathology in the appendix only ". The diseases to which he referred were terminal regional ileitis, carcinoma of the cæcum with abscess formation, acute cæcal diverticulitis, and pericæcal amœbic abscess. The purpose of this paper is to draw attention to a fifth member of this sinister community.

Acute phlegmonous cæcitis is not mentioned in most text-books of surgery, and, in those where reference to it does appear, neither the disease nor its management are described in any detail. The reports of the 21 cases, of which the main features are set out in *Table I*, were published in the medical press within the last 25 years, while the three patients whose histories are recorded at the end of this article were treated in Addenbrooke's Hospital within a period of three months. The condition, then, is by no means a common one, but it is not of such rarity that any surgeon who deals regularly with abdominal emergencies can afford to ignore its existence.

CLINICAL FEATURES

These resemble those of appendicitis very closely indeed, and acute appendicitis or appendix abscess was the diagnosis before operation in 15 of the 24 cases collected here. The age of the patients ranged from 15 to 70 years and the disease is no commoner in one sex than in the other. In the majority of the cases the length of the history was short, varying from three hours to ten days, but in two it extended over a period of years, the disease having become stabilized in a subacute phase. The pre-operative diagnoses in these two cases were cholecystitis and cæcal tuberculosis.

The syndrome of abdominal pain of recent onset and vomiting, together with tenderness and muscle spasm in the right iliac fossa, is so familiar that nothing is to be gained by its recapitulation here. In the three cases whose histories are given in detail in this paper it would have been most culpable not to have made and acted upon a pre-operative diagnosis of acute appendicitis. In two of the cases the pain was in the right iliac fossa from the start of the disease, but in one there was the classical shift from the midline to the right side which is so characteristic of appendicitis.

At operation a normal appendix is found but there are signs of inflammation in the right lower quadrant of the peritoneal cavity and a purulent peritoneal effusion is sometimes present. An indurated, thickened area is felt in the wall of the cæcum. It is usually sharply outlined, with well-defined edges, but a diffuse form, involving the whole cæcum, has been described (Spivack and Busch, 1943; Nardell, 1949). Cases with multiple lesions in the cæcum have also been reported (Barlow, 1941; Harrison, 1940). The lesion is commonly 2–3 cm. in diameter, and it may be situated anywhere in the cæcum. Its peritoneal surface is acutely inflamed with petechial hæmorrhages scattered over it, while an ulcer crater is often palpable on the mucosal aspect. This ulcer may penetrate through the bowel wall to the serous coat so that perforation into the peritoneal cavity occurs. In a few cases the indurated area in the wall of the cæcum has been so prominent that it has been palpable clinically. It has been suggested (Nardell, 1949) that the presence of a palpable mass in a patient whose history is of less than 48 hours' duration is one of the few features by which this condition may be distinguished clinically from acute appendicitis. The localized nature of the lesion, and the intense induration which characterizes it, have in the past led to an immediate diagnosis of carcinoma being made, with the result that the patient has been subjected to a needless hemicolectomy.

Microscopical examination of biopsy and autopsy specimens has shown nothing except acute inflammation spreading through all layers of the bowel wall, while bacteriological studies have revealed no specific organisms.

Numerous theories of the cause of the condition have been advanced but none are at all convincing. It is possible that, in some cases, the inflammation starts in the wall of a cæcal diverticulum, the latter being so small as to escape detection. Cruveilhier, in 1830, first drew attention to the occurrence of acute non-specific inflammatory lesions which may occur anywhere in the large bowel, and since then reports of further cases have appeared from time to time. The most recent of these is by Brownlee (1951), the site of the inflammation in his three cases being towards the distal end of the transverse colon. Brownlee labelled his cases ' acute regional colitis ' and there is, in all probability, nothing but the site to distinguish this disease from ' acute phlegmonous cæcitis '.

Table I.—THE MAIN FEATURES OF THE CASES OF PHLEGMONOUS CÆCITIS WHICH HAVE BEEN REPORTED IN THE LAST 25 YEARS

AUTHOR	SEX AND AGE	PRE-OPERATIVE DIAGNOSIS	LENGTH OF HISTORY	PRESENCE OF PALPABLE MASS	SITE OF INFLAMMATION	PERFORATION	OPERATIVE TREATMENT	POST-OPERATIVE TREATMENT	RESULT
Pétritis (1936)	F. 33	"Ventre énormément Météorisé et douloureux"	3 days	No	Anterior wall of cæcum	Yes	None	—	Death 4 days after start of illness
Cameron (1939)	M. 32	Acute appendicitis	12 hours	No	Anterior wall of cæcum 2 cm. from ileocæcal valve	No	Local excision of ulcer. Appendicectomy	—	Recovered
Harrison (1940)	M. 70	Peritonitis following suprapubic prostatectomy	—	No	Two ulcers on lateral wall of cæcum 6 cm. above ileocæcal valve	Yes	None	—	Died
Harrison (1940)	M. 32	Adhesions following appendicectomy 2 years before	3 hours	No	Medial wall of cæcum 1 cm. above ileocæcal valve	Yes	Closure of perforation and invagination. No drain	Sulphanilamide	Recovered
Harrison (1940)	F. 23	Indefinite. (Appendicectomy 10 yrs. previous)	9 days	No	Anterior wall of cæcum just above ileocæcal valve	No	Right hemicolectomy	—	Recovered
Harrison (1940)	F. 65	Spreading peritonitis	4 days	No	Five cm. above ileocæcal valve	Yes	Simple suture of perforation and closure of abdomen	—	Died
Harrison (1940)	F. 35	Chronic cæcal tuberculosis	Several years	No	"Several simple ulcers of cæcum and ascending colon"	No	Right hemicolectomy	—	Recovered
Barlow (1941)	F. 58	Acute appendicitis	24 hours	No	Posterior wall of cæcum 5 cm. above ileocæcal valve	No	Right hemicolectomy	—	Recovered
Barlow (1941)	M. 55	Perforated appendix	—	No	Two ulcers, on medial wall of cæcum above ileocæcal valve and on anterior wall	Yes	Suture of perforations, exteriorization of cæcum, cæcostomy	—	Recovered
Spivack and Busch (1943)	F. 35	Appendix abscess	10 days	Yes	Posterolateral cæcal wall	No	Appendicectomy	—	Recovered
Spivack and Busch (1943)	M. 38	Appendix abscess	6 days	Yes	Area of cæcum just lateral to anterior tænia	No	Biopsy and appendicectomy	—	Recovered
Rosser (1944)	M. 68	New growth of cæcum	18 months	Yes	Medial wall of cæcum	No	Two-stage right hemicolectomy	—	Death due to leakage at suture line
Rosser (1944)	F. 65	New growth of cæcum	3 weeks	Yes	2·5 cm. from base of appendix	No	Two-stage right hemicolectomy	—	Recovered
De Prizio (1945)	M. 33	Acute appendicitis	10 hours	No	Lateral aspect of cæcum	No	Appendicectomy	—	Recovered
Meyer and Disch (1945)	M. 35	Acute appendicitis	12 hours	Yes	"Mass in cæcum"	No	Appendicectomy and lymph-node biopsy	Intravenous sulphathiazole and blood transfusion	Died from spreading peritonitis on the eleventh day
		Acute appendicitis	3 days	No	Lateral wall of cæcum	No	Right hemicolectomy	—	Recovered

Cromar (1946)	M. 57	Acute appendicitis	3 days	No	Lateral wall of cæcum opposite ileocæcal valve	No	Right hemicolectomy	—	Recovered
McHardy and Browne (1946)	M. 56	Acute appendicitis	18 hours	Yes	Whole cæcum congested and of a rubbery consistency	No	Appendicectomy	Penicillin for 72 hours	Recovered
Bulmer (1947)	M. 22	Acute appendicitis	36 hours	No	Lower part of cæcum	No	Biopsy. No drain. Appendicectomy	Penicillin and sulphadiazine	Recovered
Nardell (1949)	—	Acute appendicitis	56 hours	Yes	Posterior wall of cæcum	No	Biopsy and drainage. Appendicectomy	Penicillin and sulphamerazine	Recovered
Nardell (1949)	M. 15	Acute appendicitis	48 hours	Yes	Posterior wall of cæcum	No	Appendicectomy. Lymph-node biopsy	Penicillin and sulphamerazine	Recovered
Riker, Gilchrist, and David (1949)	F. 61	Cholecystitis	23 years	No	Near base of appendix	No	Right hemicolectomy	Oxygen and digitalis	Recovered
Tagart	M. 62	Acute appendicitis	4 days	No	Posterior wall of cæcum	No	Biopsy and appendicectomy. Rubber drain	Penicillin and sulphamezathine	Recovered
Tagart	F. 21	Acute appendicitis	5 days	No	Lateral wall of cæcum	No	Biopsy and appendicectomy. No drain	Sulphamezathine	Recovered
Tagart	M. 59	Acute appendicitis	15 hours	No	Inferomedial wall of cæcum	Yes	Closure of perforation with over-sewing and omental graft. Appendicectomy. Rubber drain	Penicillin	Recovered

Whatever the cause, the tendency is for the condition to resolve and leave no sequelæ which are detectable clinically or radiologically. This occurred in 13 of the 24 cases in the present series, the diagnosis in all having been proved at operation. There are, however, two other ways in which the inflammatory process may evolve. It may subside into a subacute phase or it may progress to perforation with general peritonitis as a result. If the first course is followed, a mass composed of peritoneal exudate and omental adhesions forms, the clinical expression of this process being a complaint of persistent lower abdominal pain by a patient in whom a lump is palpable in the right iliac fossa. Four cases in the present series behaved in this way and it may well be that those cases of 'appendix abscess' which are operated on after an interval, and after the mass has disappeared, and in which a normal appendix is found, are, in reality, cases of subacute phlegmonous cæcitis.

Perforation, with general peritonitis, is a serious complication which carries with it a high mortality. In the present series the mortality-rate for unperforated cases was 2 out of 18 (11 per cent), while for cases in which perforation had occurred it was 3 out of 6 (50 per cent).

TREATMENT

The main surgical problem is in the management of perforation, to prevent its occurrence if it has not already happened, and to deal with it in the most effective manner once it has taken place.

Operation at the earliest opportunity is essential, not only because it is virtually impossible clinically to differentiate acute cæcitis from acute appendicitis, but also because it is the only means by which the presence or not of perforation can be determined.

From the point of view of treatment it is useful to consider separately three stages in the pathological process :—

Stage I. Perforation has not occurred and does not seem likely.—The abdomen is closed, with or without drainage, the former being the safer course. Where possible, it would be a wise precaution to suture an omental graft over the area of inflammation.

Stage II. Perforation has not occurred but seems to be imminent.—A number of possible courses are open. The whole inflamed area may be excised and the cæcum closed with a two-layer suture (Cameron, 1939); the inflamed area may be oversewn or invaginated, or the affected part may be sutured to the anterior parietal peritoneum and the wound closed around a drain.

Stage III. Perforation has occurred.—The perforation may be closed by suture and an omental graft sewn over it as is commonly done in the case of perforated peptic ulcer, or alternatively, one of the procedures suggested for Stage II may be employed. Barlow (1941), when faced with a case in which there were two perforated and two unperforated ulcers in the cæcum, closed the perforations by suture and then exteriorized the affected part of the bowel, opening it as a cæcostomy on the following day. This manœuvre was successful.

As a general rule, the simplest procedure that seems to be adequate should be employed, while the site and size of the lesion will also affect the choice.

It would, for instance, be much easier to excise or invaginate a lesion on the anterior cæcal wall than one on the posterior aspect. From the latter situation perforation into the peritoneal cavity is unlikely and wound closure with extraperitoneal drainage would be sufficient in most cases.

In every case, if there is any doubt as to the benign nature of the condition, a piece of tissue should be taken for histological examination. Provided that the state of the patient is not such that

FIG. 501.—*Case* 1. A photomicrograph of a section from the biopsy specimen. A few normal secretory glands are seen and the bowel wall is infiltrated with inflammatory cells throughout its thickness.

any avoidable prolongation of the operating time is inadmissible, the appendix should be removed as this does not seem to increase the risk.

With regard to chemotherapy, insufficient evidence is available to show whether it is useful or not, but the administration of drugs such as sulphamezathine or dihydro-streptomycin can do nothing but good. The therapeutic range of these substances covers intestinal organisms to a greater extent than that of penicillin, which should only be used for respiratory complications or if culture of a swab shows the presence of sensitive bacteria.

CASE RECORDS

Case 1.—A man of 59, complaining of abdominal pain which had been present for 15 hours. It was steady, not colicky, and made worse by respiratory movement. It was situated at first in the epigastrium, but later had shifted to the right suprapubic region. He had retched but not vomited. The bowels had been opened 3 times in the past 15 hours—solid motions. There was complete anorexia.

ON EXAMINATION.—T. 101·6° F., P. 84, R. 20. *Abdomen*: Restricted respiratory movement in the lower abdomen. There were slight guarding, tenderness, deep resistance, and release pain in the right iliac fossa. *Per rectum*: Tenderness high on the right side. No other abnormality found, apart from a slightly furred tongue and mild fœtor oris.

PROVISIONAL DIAGNOSIS.—Early acute appendicitis.

AT OPERATION.—Muscle-splitting incision in the right iliac fossa. Some slightly purulent free fluid in the peritoneal cavity. Appendix and terminal ileum normal. On the posteromedial aspect of the cæcum, and concealed by the ileo-appendiceal fold, which had to be divided, was a brown-grey slough ¼ in. in diameter, surrounded by an area of intense inflammatory induration of ½ in. diameter. Over this area the wall of the cæcum was nearly ¼ in. thick. The slough was removed with the sucker and fluid fæces leaked out of the hole which was left. A segment from the edge of the ulcer was taken for microscopical examination and the perforation closed and oversewn with thread sutures. The mesentery of the appendix, which organ was first removed, was then sewn over the area. The wound was closed in layers round a corrugated rubber drain.

POST-OPERATIVE COURSE.—He was given penicillin 100,000 units six-hourly up to a total of 2,000,000 units. Pus was discharged from the drainage hole during convalescence, but he recovered rapidly and left hospital on the seventeenth day.

FOLLOW-UP.—Two months later there was still a slight serous discharge from the wound, but no mass was felt and the abdominal wall was soundly healed. His general health was good.

Barium Enema: "The large bowel was rapidly outlined. No obstruction seen. The cæcum showed normal mucosa. No filling defects, rigidity or adhesions detected. The terminal ileum did not fill. Conclusion—normal appearance."

PATHOLOGY.—"*Biopsy specimen*: Ovoid, firm irregularly shaped piece of grey-brown tissue (1·4 × 0·8 × 0·5 cm.).

"*Microscopical appearance*: A portion of colonic wall showing intense, acute, purulent inflammation involving all coats. The mucosal surface is difficult to identify but two or three included glands appear normal in structure. A number of small, dilated veins are thrombosed. The appendix showed mild chronic appendicitis." (*Fig.* 501.)

Case 2.—A man of 62, complaining of abdominal pain which had been present for four days. The pain was in the right iliac fossa and did not radiate. It was a dull ache with colicky exacerbations and was severe enough to interfere with sleep.

For four days he had suffered from nausea and attacks of retching. He had had two attacks of diarrhœa recently, but was otherwise in good general health.

ON EXAMINATION.—T. 97·4° F., P. 80, R. 22. *Abdomen*: There was sharp tenderness over McBurney's point, with marked guarding and release pain in the right iliac fossa. Peristaltic sounds were normal. No other abnormal findings.

PROVISIONAL DIAGNOSIS.—Acute appendicitis.

AT OPERATION.—Oblique muscle-cutting incision in the right iliac fossa. The appendix appeared normal, but a hard mass was palpable in the posterior wall of the cæcum. It was the size of half-a-crown and was thought to be a carcinoma. A piece of tissue was taken for microscopical examination, the appendix removed, and the wound closed in layers. An extraperitoneal drain of corrugated rubber was inserted through a separate incision.

POST-OPERATIVE COURSE.—He was given penicillin 100,000 units six-hourly and sulphamezathine 1 g., four-hourly. He ran a swinging temperature for six days after the operation, but this subsided after a wound hæmatoma had discharged itself. He left hospital on the sixteenth day after operation.

FOLLOW-UP.—When seen a month after discharge from hospital, he was complaining of "general weakness", but nothing abnormal was found.

PATHOLOGY.—"*Biopsy specimen*: Firm, flattened, greyish-white piece of tissue with a roughened surface (1·2 × 1·2 × 0·5 cm.).

"*Microscopical appearance*: The section includes part of the muscle coat of the cæcum together with adjacent connective tissues. There is conspicuous purulent inflammation, but no evidence of carcinoma.

It is possible that the inflammation originated in a solitary diverticulum of the cæcum.

"*Appendix*: Chronic appendicitis."

Case 3.—A woman, aged 21 years, who complained of abdominal pain which had been present for five days. It was of a sharp, stabbing nature, not very severe at first, but much worse in the last 24 hours. It was situated in the right iliac fossa. There had been no vomiting and no abnormality of bowel or bladder function.

ON EXAMINATION.—T. 99·4° F., P. 108, R. 20. *Abdomen*: Tender over McBurney's point. No rigidity, but some guarding in the right iliac fossa. No release

FIG. 502.—*Case* 3. The findings at operation, showing the sharply outlined area of inflammation on the lateral aspect of the cæcum.

pain. Hyperæsthesia in the right iliac fossa. *Per rectum*: Tenderness on the right. No other abnormal findings.

PROVISIONAL DIAGNOSIS.—Acute appendicitis.

AT OPERATION.—Muscle-splitting incision in the right iliac fossa. Omentum was found presenting in the wound. Appendix not grossly inflamed. It was removed. The lateral wall of the cæcum and proximal part of the ascending colon were very inflamed and indurated (*Fig.* 502). The area was sharply defined, bled easily, and flakes of fibrin were adherent to its surface. Biopsy was performed and the wound closed in layers without a drain.

POST-OPERATIVE PROGRESS.—She was given sulphamezathine 1 g., 4-hourly. Progress was uneventful. She returned home on the ninth day.

FOLLOW-UP: Wound firmly healed. Symptom-free. *Barium enema* (three months after operation): "There was no evidence of a colonic lesion. The cæcum showed no abnormality and was freely mobile. The terminal ileum was not visualized."

PATHOLOGY.—"*Biopsy specimen*: Flattened fragment of hyperæmic, fatty tissue (2 × 1 × 0·3 cm.) with a firmer nodule (0·8 cm. diameter) at one end, overlain by white flaky, fibrinous material.

"*Microscopical appearance*: Portions of peritoneal fatty tissue show severe, acute, fibrino-purulent inflammation. No muscle or other structure from the cæcal wall identifiable.

"*Appendix*: Evidence of chronic inflammation but no apparent recent purulent inflammation in the mucosa. Fibrino-purulent inflammation in the subserous, and, to a lesser extent, in the muscle coats."

SUMMARY

Acute phlegmonous cæcitis is an uncommon condition which gives rise to symptoms and signs indistinguishable from those of acute appendicitis. It is a localized, acute inflammatory process which usually subsides, but it may progress to a subacute phase or to perforation of the bowel wall. The mortality for unperforated cases is 11 per cent, for perforated cases 50 per cent.

Treatment is directed to the prevention of perforation if this has not occurred, and, if it has, to repairing the damage.

Twenty-one cases have been collected from the surgical literature of the past quarter century and reports of 3 new cases are added.

I wish to thank Mr. V. C. Pennell for his advice on the preparation of this paper; and Dr. A. M. Barrett for the pathological reports and the photomicrograph. Mr. John Davis operated on one case and Mr. John Withycombe on another. I am indebted to the latter for the painting of the operative findings in *Case* 3.

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ARTERIOGRAPHY

A SIMPLE TECHNIQUE

By IAN MacKENZIE and H. A. R. HAMILTON

DEPARTMENTS OF SURGERY AND RADIOLOGY, WEST CUMBERLAND HOSPITALS

ARTERIOGRAPHY is no new method in the diagnosis of peripheral arterial lesions. It is used frequently in neurosurgery, but its use in those cases of arterial disease in the lower limbs which form the great bulk of the material seen by the general surgeon has hitherto been very limited. To be of value any diagnostic measure must be (*a*) accurate, and (*b*) relatively easy to perform with the equipment available in a general hospital. Various methods have been described within recent years (Learmonth, 1944; Smith and Campbell, 1948; Jones and Steiner, 1949), but each would appear to have some practical disadvantage which prevents its general use in every appropriate case. We venture, therefore, to describe the following method which we have found in practice to be both simple and accurate.

FIG. 503.—To show the position of the limb on the cassette with the X-ray apparatus in position.

TECHNIQUE

Anæsthesia.—Light general anæsthesia with suitable premedication has been used in all cases, and has given consistently satisfactory results. This form of anæsthesia is preferred to either local or spinal anæsthesia, as the former does not give assurance of complete immobility of the limb during the taking of the film, while the latter, in a nervous patient, may have to be supplemented by general anæsthesia.

Positioning of the Patient.—The patient lies supine on the operating table, with the limb to be examined placed in the following position:—

1. The hip is (*a*) fully externally rotated, and (*b*) partly abducted and flexed.

2. The knee is flexed to a right angle or rather less, and is supported by a small sandbag placed behind it.

A loaded 15 × 12 in. (or 17 × 14 in. if available) cassette is then placed in position behind the limb, resting on the sandbag. The shaft of the femur is placed parallel to one edge of the cassette and about 3 in. from it, while the leg extends across the cassette either somewhat obliquely or parallel to its other side (*Fig.* 503). Care is taken when placing the cassette in position that it is pushed as high up as possible behind the buttock, while making sure that the whole limb as far as the lower third of the leg lies on the cassette. We have used only 15 × 12 in. films, but greater ease in placing the limb in position would be obtained by using 17 × 14 in. films. With the limb in this position the entire arterial pattern from the upper third of the thigh to the middle of the leg can be recorded on one film.

When it is necessary to visualize the arterial circulation of the lower half of the leg the following simple modification can be employed. The limb is placed in position, as described above, and the 15 × 12 in. cassette is placed behind it with the longer edge parallel with the femur. A paper-wrapped 15 × 6 in. or 12 × 6 in. Ilfex or Kodirex film is placed in the axis of the leg, the upper part of the film being placed between the limb and the lower part of the cassette, and so overlapping part of the limb covered by the latter. The shadow of the paper wrapping of the Ilfex film is barely perceptible on the film taken in the cassette; and by removing one of the intensifying screens of the cassette and increasing the exposure by approximately one-third, very similar densities are obtained on the two films.

In order to cover the entire limb in this way, the anode-film distance must not be less than 30 in. and should preferably be somewhat greater.

Radiography.—The following types of X-ray apparatus have been used: (1) Dean Mobile Unit (30 ma.); (2) Newton Victor F.4 Portable.

While the mobile unit has the greater output, the portable unit has given good results and has the following advantages: (*a*) Greater ease in the handling, positioning, and angulation of the tube; (*b*) less room is taken up in the operating theatre; (*c*) the tube column permits a 30 in. anode-film to be used, which lessens any tendency to distortion.

A cone is not used.

The apparatus is placed in position on the opposite side of the operating table to the limb being examined, and is carefully centred, the centring point being slightly inside the bend of the knee.

Exposure of the Artery.—The limb is prepared for operation, using 90 per cent alcohol, and towels are placed in position with the minimum number of towel clips.

The incision is made across the common femoral artery parallel to and just below the inguinal liga-

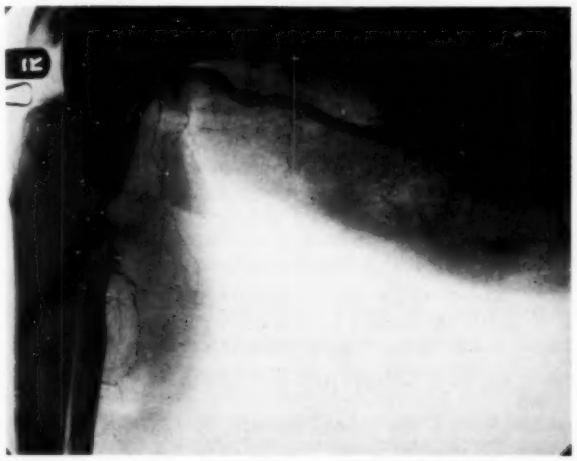

FIG. 504.—Shows a normal arteriogram of the lower limb.

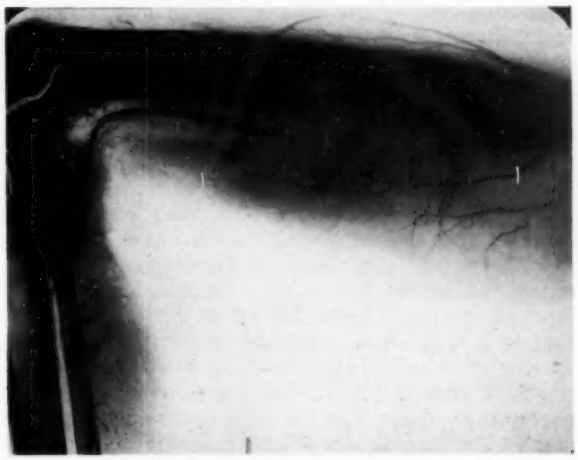

FIG. 505.—Showing obliteration of the proximal half of the superficial femoral artery.

FIG. 506.—Showing obliteration of the popliteal artery.

FIG. 507.—Showing obliteration of the whole of the superficial femoral artery and of a considerable portion of the popliteal artery.

ment, and the vessel is clearly exposed; it is not interfered with in any way prior to the injection.

Complete hæmostasis having been secured, all instruments are then removed from the operating table.

Arteriography.—We have used a 70 per cent solution of diodone for the injection (Pyelosil 70, the dynamic viscosity of which at 40° C. is 35 millipoises) and have found it to give consistently good results. A transient general reaction is noted (which adds to our preference for general anæsthesia), but the solution has no local irritant effect. Twenty c.c. of the solution are placed in a syringe with an eccentric nozzle carrying a No. 18 or No. 19 serum needle. It is convenient to bend the needle in the middle, so that the bevel is on the outer side of the arc. The point of the needle is carefully inserted through the vessel wall, bevel downwards, in a *proximal* direction and the solution is injected *centrally* into the artery at a rate of approximately 1·5 c.c. per second. In practice it is convenient for the operator to count aloud slowly up to ten, keeping a steady pressure on the plunger, by which time 15–16 c.c. of the solution will have been injected. At the count of 'ten' the radiographer makes the exposure.

The needle is then withdrawn and any oozing from the puncture hole is controlled by gentle pressure with a swab. The cassette is removed and the film is developed at once and brought back for inspection, when, if it is satisfactory, the wound is sutured. Should it not give the required information the injection can be repeated, after replacing a loaded cassette. The whole operation can, with practice, be completed within twenty minutes and, if necessary, the opposite limb can be examined in similar fashion at the same sitting.

DISCUSSION

Learmonth (1944) has succinctly summarized the various peripheral vascular conditions in which arteriography can be of value. In civilian practice

the vast majority of cases of peripheral vascular disease which present themselves for treatment are included under the general description of obliterative vascular disease of the lower extremities. In many, the extent of the disease can be assessed summarily, when gangrene or a pre-gangrenous condition is present, but there are also a considerable number of patients in whom the exact position and extent of the obliterative process can only be assessed in general terms. Among these, cases presenting with the symptoms of intermittent claudication form a notable group. Clinical observation of the presence or absence of the arterial pulse at different levels in the affected limb gives a general indication of where the block in the main arterial trunk may be, but more precise information of its exact position and extent is obviously desirable, as also is a knowledge of the extent of the collateral circulation. Arteriography yields such information, but its more general use depends on the availability of a method which requires no elaborate apparatus and which gives an accurate picture of the condition of the arterial system of the limb. In the method described we believe that these criteria are complied with; it involves the attendance of one radiographer, the use of one mobile (or portable) X-ray unit, and one 15 × 12 in. film for each limb. Its disadvantages as compared with the ideal method are the use of a general anæsthetic and the necessity for making a surgical incision. The reason for the former has been discussed. With regard to the latter, we feel that the depth of the common femoral artery from the surface is such that any percutaneous method of injection would require considerable and continuous practice, and would not be free from the possibility of error.

We have not found any complication to follow the method as described, and the patient can be ambulant within twenty-four hours.

The illustrations (*Figs.* 504–507) indicate the results of the method in some typical cases.

We are indebted to our radiographer, Mr. C. N. Tomlinson, for the photograph in *Fig.* 503.

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A METHOD OF ANGIOCARDIOGRAPHY

By IAN M. HILL, LONDON

SINCE Robb and Steinberg (1939) developed angiocardiography on a practical scale, its use as an investigation, particularly of congenital heart anomalies, has spread widely. Quite apart from its value as an adjunct in diagnosis of the type of malformation, it is increasingly important in delineating the anatomical features of the heart chambers and outflow tracts (Baker, Brock, Campbell, and Suzman, 1949). Since Brock (1948) stressed the question of direct operation for the relief of pulmonary valvular stenosis, and introduced, as a practical measure, infundibular punch resection where the infundibular stenosis is predominant (Brock, 1949, a, b), an accurate demonstration of endocardiac anatomy has become essential. This can only be obtained by radiological contrast media. Cardiac catheterization may be of great help as a diagnostic measure; but it is rarely possible to demonstrate the exact site and nature of the stenosis (Holling and Zak, 1950). So helpful does the surgeon find angiocardiography, that it is now a routine at this clinic on all cases of congenital morbus cordis considered for operation, unless the risk is believed prohibitive.

Angiocardiography has been used in over 150 patients at Guy's Hospital, so it seems worth recording the surgical and general technique and methods personally used in a series of 120 cases. During the series various minor technical modifications were made; but the basic technique has remained unchanged and has been found reliable. The X-ray apparatus used in all but two cases has been described by Hills (1948).

Nature of the Investigation and Risk.—Angiocardiography is often regarded as an investigation without risk. This is not so in congenital heart disease. In the present series there were three deaths, two of which have been reported by Campbell and Hills (1950). In addition to these, one mentally retarded child of 5 has suffered permanent anoxic cerebral damage with persistent athetoid movements.

It is therefore important that all concerned should realize the risk and believe that only constant vigilance by every member of the team will enable the mortality and morbidity to be kept to a minimum.

Preliminary Investigation and Assessment.—All cases will have been submitted to a full clinical cardiological scrutiny, and the patient's physical condition, capabilities, and history will give an indication of the risk attached (Campbell and Hills, 1950). A history of attacks of unconsciousness is particularly indicative of a high risk.

Many of the children suffer from chronic upper respiratory tract infection and recurrent pyrexia, which do not settle until after the corrective operation. These conditions are no bar to angiocardiography, nor to general anæsthesia; but the knowledge of this should not engender a complacency of acute exacerbations of respiratory tract infection.

The surgeon performing the investigation should always visit the patient beforehand and, with the help of the ward staff, estimate the degree of co-operation which may be expected. In adults, local analgesia is used; in children under the age of 10 years, always a general anæsthetic. Phlegmatic

adolescents may well tolerate local analgesia if the procedure is carefully explained.

It is felt that the reduced oxygen consumption under the near basal conditions of general anæsthesia and the added facility of high concentration oxygen administration, intubation, and resuscitation, cause general anæsthesia to be a lesser risk in children and apprehensive adolescents than local analgesia. The administration of the anæsthetic to these patients is, however, a very specialized task (Rink, Helliwell, and Hutton, 1948; Rink, quoted by Campbell and Hills, 1950; Carnegie, 1951), and the services of an adequately experienced anæsthetist are a *sine qua non*.

Patients undergoing extensive cardiac investigation may well have been subjected to heavy irradiation (Hills and Stanford, 1950) and inquiry should be made to ascertain the extent of recent radiography and screening.

It is customary to carry out an oral sensitivity test with the particular brand of diodone being used for the injection. In practice it is easier to persuade children to suck a tablet of the preparation rather than to retain the unpleasant fluid in the mouth. If no paræsthesiæ are experienced after retaining the tablet in the mouth for one minute, the patient swallows it, and if no nausea or vomiting follows, the patient is regarded as having no hypersensitivity to the drug. No case of hypersensitivity has been detected in this series.

Premedication.—For general anæsthetic oral nembutal, $\frac{1}{2}$ gr. per stone of body-weight, one and a half hours before, and atropine, $\frac{1}{100}$ gr. half an hour before, have been used in most of the cases. More recently rectal thiopentone (dose 1 g. per 50 lb. body-weight) and atropine $\frac{1}{100}$ gr. half an hour before, have been used with success.

For local analgesia, oral sodium phenobarbitone, 2–3 gr. two hours beforehand, was found to be the most suitable drug for producing a placid patient who will carry out instructions.

Ward Arrangements.—All patients leave the ward on a trolley, whether being investigated under local or general anæsthetic, and are accompanied by a trained nurse, a full cylinder of oxygen, an efficient flowmeter, and a facepiece fitting sufficiently well to administer a high concentration of oxygen.

Angiocardiography is carried out in the X-ray department frequently on patients from medical wards. Staff here are not familiar with the handling of patients recovering from anæsthesia and this calls for additional vigilance on the part of all concerned.

Returning from the X-ray department, the anæsthetist should accompany the patient to the ward and remain until he is satisfied that all is well. The administration of oxygen on this journey is a necessary safeguard, and it is unfair to expect nursing staff to be as competent in this matter as a trained anæsthetist; it is in the dimly lit corner during the unexpected wait for the lift that anoxia may occur with tragic results.

On returning to the ward the patient is immediately placed in an oxygen tent (or, if conscious, a well-fitting B.L.B. mask may be used) and efficient oxygen administration is continued until full recovery.

Arrangements in the X-ray Department.—Every facility must be given to the anæsthetist in the matter of space, illumination, and quiet for the patient. When anæsthetized, the patient is placed in position on the X-ray table (usually supine) and a trial exposure made to ensure that all the apparatus is working efficiently. If the electrocardiogram is being used to check the cardiac rhythm, leads are attached and a trial tracing taken (Reynolds, 1951). If local analgesia is used, the process of injection, the noises of the apparatus, and the breathing instructions are explained to the patient. It is important to warn patients that they will experience a feeling of extreme

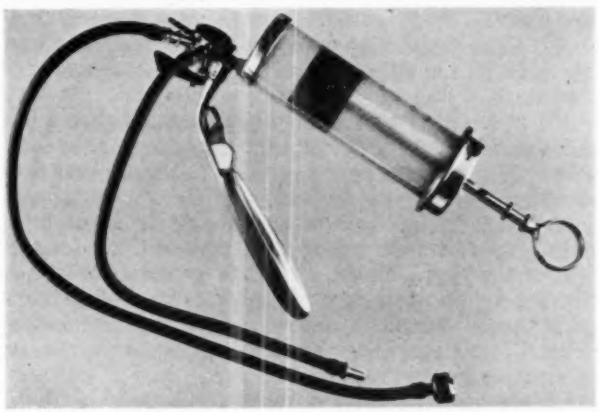

FIG. 508.—The syringe used for angiocardiographic injection.

heat and flushing and that self-control will be required to hold the breath during the last few exposures. Finally, the agreed signal for injecting is checked with the operating radiologist or technician.

The Injection.—Full aseptic precautions are employed throughout. The surgeon and assistant are fully gloved and gowned. Adequate illumination must be provided. The surgeon, assistant, and anæsthetist wear radio-opaque protective aprons.

The skin area is sterilized, the arm surrounded with sterile towels, and the local anæsthetic injected both intradermally and about the vein. This is used even with general anæsthetic, as it reduces venespasm and gives an avascular field. The veins of choice are the basilic at the right elbow, the cephalic in the right upper arm or at the right elbow, or the similar veins in the left arm. The site chosen may be modified by previous venepuncture, with hæmatoma, catheterization, or suspected caval anomalies. In small children, where the arm veins are too friable or deeply placed in fat, the external jugular vein has been used with success.

The skin is incised over the vein, which is displayed, lifted on an aneurysm needle, and a hole cut in it just large enough to accommodate the cannula. This is inserted with a sharp trocar in place and the latter withdrawn as soon as the vein lumen is entered. The cannula most commonly used has a bore of 0·224 cm. and a length of 8 cm. It is essential that there should be no perceptible shoulder between the trocar and cannula and yet the trocar should be sufficiently slack to allow easy withdrawal.

The loaded syringe is attached to the cannula and the whole held firmly in place and the patient's arm abducted to place the surgeon's hands as far out of the X-ray beam as possible (Hills and Stanford, 1950).

The syringe used, a three-way blood transfusion syringe, is shown in *Fig.* 508, and it fulfils the following requirements :—

1. It has a large outflow tract (fullest bored-out S.I.M.A. mount) to permit rapid emptying.
2. The contents may be rapidly changed and the syringe reloaded without removing from the cannula.
3. It may be firmly held to the arm with one hand and the cannula kept in line with the vein even if the patient moves.
4. It may be of either 50 ml. or 100 ml. capacity barrel.
5. It is simple to work, withstands sterilization by boiling, is robust, and easily dismantled for cleaning.

It is felt that the more rapid delivery through a short wide intravenous cannula is preferable to using a longer polythene tube giving a slower delivery nearer the heart.

The technique of cutting down is used as a routine as it results in a more rapid and sure insertion of the cannula ; it is more economical of veins ; the incidence of hæmatoma formation before cannalization is smaller ; and the likelihood of extravenous injection is less than with blind percutaneous venepuncture.

When the anæsthetist regards the patient's condition as stable and the electrocardiographer reports a steady rhythm, a trial injection of 10 ml. is made to estimate the freedom of vein flow. Initially normal saline was used in the syringe for this purpose ; but more recently, procaine 0·2 per cent in isotonic glucose has been used following the experience of the stabilizing action of this drug during direct cardiac surgery (Carnegie, 1951, quoting Whytehead). Evidence of cardiac irritability may call for further intravenous procaine before the diodone injection.

The syringe is then emptied by the third channel and refilled from the second with warmed 70 per cent aqueous diodone of the volume to be injected. No attempt has been made in this series to use a formula for estimating the volume of dye used, and previous experience is the only guide. The factors to be considered are the age, size, weight, chest size, disability, and the nature of the cardiac lesion. The dose has varied from 25 ml. in a severely disabled child of 4 to 80 ml. for a large adult.

Whatever the dose used, the injection should be completed in under 2 sec. and preferably under 1·5 sec. When using the 100-ml. syringe with a dose of over 60 ml. this requires the firmest pressure that can be placed on the piston by the operator's thumb.

Before the injection, the conscious patient is given final breathing instructions, or the anæsthetist places the protective glove on the hand holding the mask, and the starting signal is given by the injector so that the radiologist is prepared to make the first exposure as the plunger moves down the syringe.

When all the films are taken, the syringe is refilled with saline or procaine-glucose solution and the vein irrigated to remove the stagnant diodone and thus lessen the risk of vein thrombosis. If necessary, the vein may be kept open by the slow injection of saline before a second injection for a different position. The second injection is not made unless reports from the anæsthetist and the electrocardiographer are satisfactory. The cannula is then removed and a skin stitch inserted whilst pressure is maintained on the vein to prevent oozing. The vein is not ligated unless in the neck, and a firm pressure dressing applied. With this technique, the vein is often seen to be patent two weeks after the injection.

Cardiac Irregularities.—Oxygen administration by the anæsthetist is carried on until the heart beat is clinically and electrocardiographically normal. Cardiac irregularity not responding to adequate oxygenation is first treated by further intravenous procaine. Cardiac arrest has been dealt with by direct left ventricular percutaneous puncture and the injection of 0·5 ml. liquor adrenalini. A syringe containing 1 ml. adrenaline solution and an 8-cm. needle is always available on the trolley for this purpose. Direct cardiac massage has not been attempted in the three fatalities occurring in this series ; but it might well be considered advisable as an immediate measure and in this case sterile thoracotomy instruments should always be held available.

SUMMARY

A method of angiocardiography used in 120 cases is described in detail, together with the precautions taken to reduce to a minimum the mortality which may be expected when investigating serious cases of congenital morbus cordis.

I wish to express my gratitude to Dr. Maurice Campbell and Mr. R. C. Brock for referring the cases and for their constant encouragement ; to Dr. T. H. Hills, the Sister, and staff of the medical X-ray department of Guy's Hospital for their unfailing and generous help ; to Drs. E. H. Rink, P. J. Helliwell, A. M. Hutton, and D. M. Carnegie for giving the anæsthetics in conditions which were often cramped and difficult ; and to Dr. G. Reynolds for giving so much of his time to the production of continuous electrocardiograms.

The syringes were made for me by Messrs. A. L. Hawkins, of 15, New Cavendish Street, W.1.

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KIDNEY HOMOTRANSPLANTATION*

By W. J. DEMPSTER, F.R.C.S.E.

DEPARTMENT OF SURGERY, POSTGRADUATE MEDICAL SCHOOL OF LONDON AND THE BUCKSTON BROWNE RESEARCH FARM, DOWNE, KENT

It has been the experience of all past research that kidneys disintegrate within a few days of being homotransplanted. This, at least, is the evidence from animal experiments (*see* reviews by Ibuka, 1926; Williamson, 1926; and Wu and Mann, 1934). From some accounts it appears that an occasional kidney has survived many days—26 days (Dederer, 1920), 35 days (Carrel, 1908), and 71 days (Avromovici, 1924). The average length of survival, however, has usually been reported as being about four days.

The clinical application of kidney homotransplants would open up a new field in surgery. There are many chronic diseases of the kidney which are, at the moment, without cure. It is in the chronic group of cases that homotransplantation of kidneys would be necessarily first applied; there would appear to be no indication for this procedure in the acute anurias which are amenable to medical and dietetic measures. While it may be heroic surgery to attempt, at this juncture, kidney homotransplants in the human, it is unwise to carry out such procedures without any scientific knowledge of the fundamental processes involved. When all the evidence of the nature of the disintegration of homotransplanted tissue is borne in mind, it is quite out of the question that kidneys should be homotransplanted in man just in case a permanent survival might be obtained. The report of Lawler, West, McNulty, Clancy, and Murphy (1950) of a homotransplanted kidney surviving for some months in a human female, has turned out on closer examination by neutral observers to be unproven. Attempts at homotransplanting kidneys in humans in France have had no more success than the animal experiments of the past fifty years (Servelle, Soulié, Rougelle, Delahaye, and Touche, 1951; Dubost, Oeconomos, Vaysse, Hamburger, Milliez, and Lebrigand, 1951, a, b; and Kuss, Tinturier, and Milliez, 1951).

The Nature of the Problem: the Biological Incompatibility of Tissues.—It was realized as far back as 1910 that autotransplantation of kidneys in animals being a surgical feasibility, the disintegration of a homotransplanted kidney, after a few days in a host, was for reasons other than technical. The nature of the biological incompatibility of homotransplanted tissue remained obscure, however, until the recent researches of Medawar (1944). The evidence from Medawar's experiments suggested an actively acquired immunity on the part of the host as being the fundamental process in the disintegration of homotransplanted tissue. The various theories put forward to explain the disintegration of homotransplanted tissues have recently been reviewed (Dempster, 1951). For the purposes of this communication, the theories of local and systemic immunity will be considered in some detail.

The Theory of Local Tissue Immunity.—Previous workers have described the disintegrative process in the homotransplanted kidney in terms of a local cellular reaction. The histological findings, however, have never been seriously analysed. The last published account of the histological changes occurring in the homotransplanted kidney is that of Wu and Mann (1934). These authors are noncommittal about the origin of the cellular reaction in the kidneys they homotransplanted, but, as they pay passing reference to Loeb's concept of a local immunity, one can only conclude that they accepted to some extent the theory that the local cellular reaction was a manifestation of a purely local immunity developed between the kidney and the immediately surrounding tissues of the host. This concept of Loeb has dominated the work on homotransplantation of tissues for about half a century; Loeb (1945) has expanded his concepts to cover the widest range of immunological phenomena. The evidence from Medawar's experiments, however, requires a new critical evaluation of the nature of the disintegration of the homotransplanted kidney. Medawar (1944) and Dempster, Lennox, and Boag (1950), in their work on homografted skin in rabbits, denied any significant local mesenchymal cell reaction accompanying the disintegration of the homografts. However, there is no doubt whatsoever that a round-cell infiltration does occur in the process of disintegration of kidney homotransplants. Thus, the main point at issue now is this: is the cellular reaction observed in disintegrating homotransplanted kidneys a purely local reaction of the host tissues, or is it a manifestation of a general systemic reaction on the part of the host? Or, is it renal in origin and merely a response against the host? And what is its relationship to the disintegration of a homotransplanted kidney?

Loeb (1945) has accumulated so massive an amount of data on homografting and homoimplanting, that it is perhaps beyond the ability of any one person to review it adequately. Though it may be unfair, therefore, to reduce his erudite volume to a few sentences, yet, from the immediately practical point of view, this must be done.

Loeb maintains that a host reacts in a purely local way against homotransplanted tissue. The local cellular infiltration is interpreted by him as "... being caused by the difference in the individuality differentials of host and transplants, these cells being attracted by the strange individuality differentials of the grafted tissue; their presence indicates the existence of variable degrees of incompatibility between tissues and the action of a mild rather than that of a severe, acutely acting toxin". These differentials, it must be granted, are rather 'strange'; most people call them antigens! These differentials would appear to be rather unnecessary postulates, for Loeb goes on to say that "... these

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differentials may also act as antigens and induce the formation of immune substances which then may secondarily intensify the strength of the reactions ".

Loeb and his school were dependent on a purely histological interpretation of the changes in tissues because he and others restricted themselves to homo-implanting pieces of kidneys and other organs (Loeb, 1917, a; Fleisher, 1917). Attention has already been drawn to the serious defects of attempting to interpret the processes of tissue incompatibility by

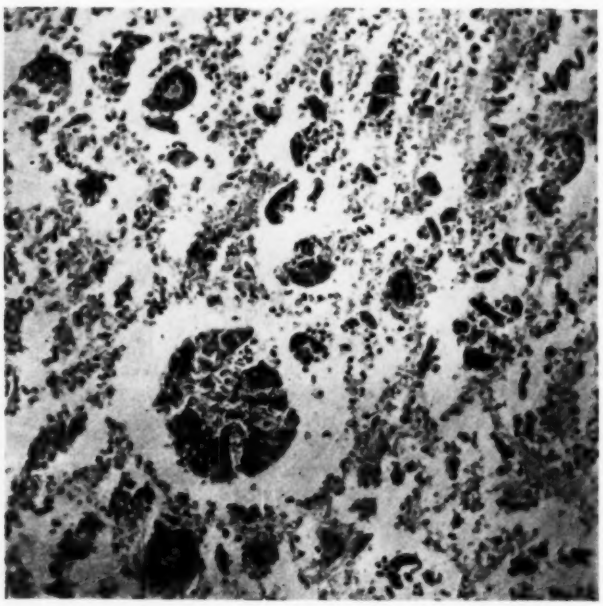

FIG. 509.—Section of a piece of kidney auto-implanted subcutaneously twenty-four hours previously. Shows complete necrosis. (H. and E.) (× 155.)

the technique of implanting pieces of organs (Dempster, 1951). A point relating to definition might profitably be interposed here. The procedure of transferring tissues from one site to another without effecting an immediate blood-supply should be referred to as implantation; grafting is the best word for skin transfer. Transplantation should be reserved for the transfer of organs to which a blood-supply is effected immediately and implying some degree of surgical skill. This aspect of the problem can be dealt with at this juncture as it is fundamental in the rejection of Loeb's theory.

Fig. 509 shows a photomicrograph of a piece of kidney auto-implanted subcutaneously in a dog and removed after twenty-four hours; complete disintegration is obvious. *Fig.* 510 shows a photomicrograph of a section of a kidney which looks normal; in this case, the whole kidney was auto-transplanted to the neck of a dog, where it was interposed on the carotido-jugular circulation using a technique already described (Dempster, 1950). This demonstrates that false impressions can be gained about the behaviour of tissues when transferred from one part of the body to another if implantation techniques are used. It is on this false basis that Loeb has built up the concept of local cellular reaction; the autotransplanted kidney (*Fig.* 510) shows no cellular reaction, but Loeb's auto-implanted contr's all show some degree of cellular reaction around t e necrotic pieces of homo-implanted kidney (Loe , 1917, a).

The basic defect of Loeb's local immune reacti n is that it is incapable of dealing with the ho - homotransplant relationship in any active, dynan c way. His theory implies a somewhat passi e behaviour on the part of the foreign tissue (t e liberation of ' differentials ', for instance, being s

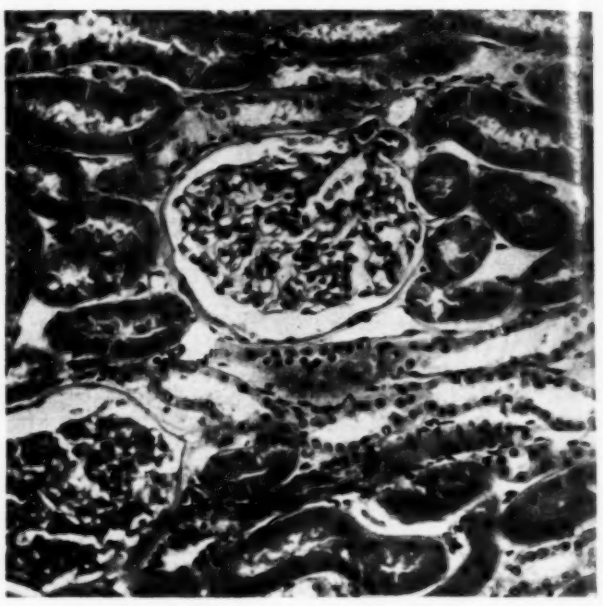

FIG. 510.—Section from an autotransplanted kidney removed while still functioning after two months in the neck of a dog. The architecture is essentially normal. (H. and E.) (× 170.)

only activity), whereas one should seek methods which will reveal a mutual interplay between host and foreign tissue. It will be shown in this communication that no support can be extended to Loeb's theory on experimental grounds.

The Theory of an Actively Acquired Immunity.—Skin is the ideal tissue with which to elucidate the immunological problems involved in homotransplantation of tissues because of its few technical variables, a vascular supply develops quickly, and skin is a tissue which can be accurately and easily controlled by autografting—a routine procedure in plastic surgery units. It was with the skin of rabbits that Medawar (1944, 1946, and 1948) showed quite clearly that the fundamental process involved in the disintegration of skin homografts was the development in the host of an actively acquired immunity. That is to say, an antigen-antibody reaction in some way inhibits the growth of the homografted skin; a second crop of skin-grafts from the same donor to the same host will die much quicker than the first. This implies, therefore, that naturally occurring antibodies are not responsible for the disintegration. It might be objected that the tissue of the rabbit is not a satisfactory basis on which to build any immunological theory because of the rabbit's uniqueness in exhibiting the Arthus phenomenon so intensively. Thus, one purpose of

this communication is to present evidence suggesting that the cause of failure of homotransplanted kidneys in dogs is due to an actively acquired immunity on the part of the host. The kidney is not an easy organ to study from the immunological point of view in this context; at the same time, it is the only organ to which one can easily effect a blood-supply and whose physiological behaviour one can easily study and control.

In elaborating the process by which the host rejects the homotransplanted kidney, it will be important not to lose sight of the fact that such a kidney is by no means a passive organ. It will be incumbent upon us to analyse very carefully all changes which the kidney may undergo—and it will be necessary to keep in mind that the homotransplanted kidney itself may be taking part in its own destruction. As the homotransplanted kidney, for a time, is an active physiological unit, it is only reasonable to suppose that its reticulo-endothelial system is functioning equally well. Thus, any infiltrating cells which one may see in the disintegrating homotransplanted kidney may be of renal and not of host origin. This is a situation not adequately faced up to by Loeb. For these reasons it has been considered most important to correlate function with morphology before any definite conclusions could be drawn about the nature of the disintegrative process in homotransplanted kidneys.

If one correlates function and morphology, no serious conclusions can be drawn from the histological features of pieces of homo-implanted kidneys. Not only is the dynamic process of tissue incompatibility under such circumstances completely lost, but one learns nothing about the physiological behaviour of kidneys transferred to another host which, of course, is exactly what we want to examine in detail. Furthermore, implantation of pieces of organs masks the great number of purely surgical problems encountered in organ homotransplantation. In this respect, another defect of Loeb's approach is to be seen in his work on blood incompatibility (Loeb, 1917, b) in which he tried to solve the problem by implanting pieces of blood-clot. By the same token, no histological considerations can be extended to those homotransplanted kidneys which were the site of surgical accidents such as arterial thrombosis, venous congestion, or what will be described later as the 'anuric kidney'. Such results may be excluded from any analysis of tissue incompatibility but not from any given series of operations, as thereby a false impression might be gained about the lack of surgical difficulties involved in kidney homotransplantation in my hands.

MATERIALS AND METHODS

Greyhound bitches (weights 21–25 kg.) were used in all experiments because the kidney of the mongrel dog is very often the site of infection and accordingly the histology of the homotransplant reaction is complicated beyond interpretation (Dempster, 1953). The anæsthetic used was intramuscular nembutal in doses of ½ gr./kg. body-weight. Antibiotics employed included: penicillin, streptomycin, chloromycetin, and terramycin.

The technique of transplanting kidneys to the neck of dogs has been described in detail elsewhere (Dempster, 1950). End-to-end anastomosis of the renal vessels on the carotido-jugular circulation was effected by 5/0 silk sutures, using the Carrel technique. The method of collecting urine was as described previously (Dempster, 1950; Dempster and Watson, 1951).

Some details of the operation need elaboration. On cutting the renal artery and removing the kidney from the donor dog, it is important immediately to place a small bulldog clamp across the bifurcation of the renal artery. The length of the renal artery proximal to the clamp is now exposed to the atmosphere and usually a small blood-clot forms quickly and must be flushed out with saline. By having the clamp across the renal artery, no saline enters the kidney nor does the clot get pushed on; on no account should the kidney be flushed out with saline; no evidence was ever found to suggest that intrarenal thrombosis occurs during the period of transfer from donor to host. The use of liquid paraffin should be limited to the silk; if liquid paraffin is used liberally, as is the custom in aortic anastomosis, there exists a great danger of liquid paraffin entering the kidney and blocking the glomeruli. Spasm of the renal artery was encountered in the beginning, and this was probably due to too tight and too many sutures in the anastomosis; the renal artery is very sensitive to drag. In spite of all possible precautions, there was a considerable incidence of anuria, which may be related to severe nerve stimulation of the renal artery when the kidney was being mobilized.

General Plan.—The general plan of the experiment is as follows:—

1. Kidneys were homotransplanted to the neck of dogs whose own kidneys were left intact; in some cases, one kidney was removed from the host.

2. Kidneys were homotransplanted to the neck of dogs whose own kidneys were removed simultaneously.

3. Successive homotransplants: following the disintegration and removal of the first kidney, the second kidney from the *same donor to the same host* was homotransplanted. For this experiment, two dogs were usually, but not always, used in pairs. Thus, after the first operation, each dog had a homotransplanted kidney in its neck and one of its own kidneys in its belly; and, after the second operation each dog had then a homotransplanted kidney only.

4. Successive homotransplants: following the disintegration and removal of the first homotransplanted kidney, a second kidney from *another dog* was homotransplanted to the *same host*.

5. Successive homotransplants: the first homotransplanted kidney was removed after twenty-four hours in the host, and then the second kidney from the same donor to the same host was homotransplanted.

6. The kidneys of the future donor dogs were irradiated twenty-four hours before homotransplantation. In some dogs, one irradiated kidney was retained as a control of the irradiation effects. At the time of operation, para-aortic lymph-nodes, when found, were removed for histological study of the effects of irradiation.

7. Twenty-four hours before the host dogs were due to receive a kidney, they were given total body irradiation.

8. Serum cross-transfusion : after the disintegration of the first homotransplanted kidney, blood was withdrawn from the host and transfused back into the original donor dog. On two occasions following this, the second kidney from the same donor to the same host was homotransplanted. Biopsies were taken from these second kidneys before the circulation was opened up in the neck ; the biopsy areas were plugged with a piece of muscle.

Irradiation Technique.—The irradiation was carried out by Dr. J. W. Boag, of the M.R.C. Radiobiological Unit, Hammersmith Hospital. The details of the irradiation techniques will be described in a subsequent communication dealing particularly with irradiation effects on homotransplanted kidneys. The dose of total body irradiation was about 150 r ; the local irradiating dose to the kidney region was about 250 r.

Nephro-arteriograms.—In 10 cases, after the homotransplanted kidney had stopped secreting, the animal was anæsthetized and the kidney was removed from its bed in the neck. A needle was then placed in the carotid artery and 3 ml. 50 per cent pyelosil was injected quickly and gently and a picture taken at varying intervals. Controls in autotransplanted kidneys which were functioning were also taken.

Methods used for obtaining Histological, Bacteriological, and Other Data.—Sometimes biopsies were removed at varying intervals after operation but usually this was avoided for fear of infecting the kidneys. When the homotransplanted kidneys were deemed to be in the process of disintegration, which usually coincided with the development in the host of a toxic syndrome described elsewhere (Dempster, 1950, 1953), the dog was anæsthetized and the kidney mobilized in the neck. There was usually no attempt on the part of the host tissues to heal around the kidney, but the skin wound over the kidney healed satisfactorily. It was invariably found that the pulsations in the renal artery were much less than at the original operation. The impression that the renal circulation was reduced was verified : (1) By compressing the renal vein ; the normal kidney is extremely sensitive to this procedure—the disintegrating homotransplanted kidney is not sensitive to this and takes some time to distend ; and (2) On cutting the renal vein, one noted the meagre outflow of blood from the kidney.

After this preliminary examination, the carotid artery was cut and the kidney then gently compressed to clear out as much blood as possible. The kidney was then weighed. Afterwards, a hot metal rod was applied to an area of the kidney and allowed to sear the capsule ; through this seared area a sterile swab was pushed into the kidney substance. This swab was later examined directly and cultured for growth of aerobic and anaerobic organisms. The kidney was now opened and inspected ; sections were removed and fixed in formol saline. The whole procedure took about five minutes.

The stains employed included : hæmatoxylin and eosin, picro-mallory, azo-carmine, allochrome, and methylgreen-pyronin-orange G.

Successive Homotransplants.—In those experiments where two kidneys were homotransplanted to the same host from the same or a different donor, the procedure has been referred to previously as successive homotransplantation. It is on the basis of these successive homotransplant experiments that evidence will be presented suggesting that the disintegration of the second kidney, from the same donor to the same host, occurs at a faster rate than the first kidney. On the other hand, the second kidney from a different donor to the same host will be shown to survive for as long as or for longer than the first kidney. This, then, is the kind of evidence required to be demonstrated if one is to substantiate the theory of an actively acquired immunity as being the process involved in bringing about the disintegration of homotransplanted kidneys.

Difficulties encountered.—There were many difficulties involved in obtaining even a short series of successive homotransplanted kidneys where both the first and second kidneys came from the same donor. These were :—

1. Vascular anomalies in one or other kidney. In the dog, on the left side, the arterial supply to the kidney is often in the form of two independent renal arteries ; this prevents end-to-end anastomosis to the carotid artery of the host. For this reason the left kidney in this type of experiment should always be used first if satisfactory or the experiment abandoned with that particular dog if an anomaly exists.

2. Renal anomalies in one or other kidney—congenital aplasia, lobulation, and cysts.

3. Severe scarring due to past infection.

4. Occasional death of the donor or recipient after the first operation.

5. Arterial thrombosis or acute venous congestion in the first or second kidney soon after operation.

6. The ' anuric kidney ' which will be described later.

Therefore, before any conclusions, histological or immunological, could be drawn, one had to observe the natural histories of two successive homotransplanted kidneys from the same or different donors to the same host in which the cause of the disintegration was for reasons other than technical.

RESULTS

The Clinical Course of a Homotransplanted Kidney in the Neck of a Dog.—Urine flows from the homotransplanted kidney (as from the autotransplanted kidney) within fifteen minutes of opening up the carotido-jugular circulation. The dog usually recovers well from the operation within twenty-four hours, by which time the kidney is secreting freely and as fast as it will ever secrete. The length of survival varied within a period of 2–12 days. In the vast majority of cases before the introduction of terramycin, a toxic syndrome developed in the dog and this usually coincided with the cessation of urine flow from the homotransplanted kidney (Dempster, 1950, 1953). This syndrome was characterized by high fever, apathy, and disinclination for food and water. Infection plays an important part in this syndrome and bacteria were cultured from such kidneys. However, it was thought that infection occurred as a result of some biological change in the kidney which favoured localization of bacteria circulating in the blood-stream. It will be seen that dogs in *Table II* (those bilaterally nephrectomized) did not develop a toxic state ; it would appear that the developing

uræmia prevents the development of a pyrexia in dogs with no intact kidneys of their own. It was the rule, without exception, that with arrest of function of the homotransplanted kidney, bilaterally nephrectomized dogs developed hypothermia—a finding which is confirmed in veterinary practice in relation to uræmia.

The ureter and pelvis of the homotransplanted kidney in the neck become swollen, as has been described previously in the autotransplanted kidney (Dempster, 1950).

A dog with a good functioning homotransplanted kidney behaves normally and for a few days enjoys good health. Later, however, even although the volume of urine is high the dog shows signs of developing uræmia (should it be bilaterally nephrectomized) and all food is refused; the blood-urea at this stage is raised. When the kidney stopped secreting, whether in association with a toxic syndrome or not, the kidney was removed. On removing such a kidney from the neck, it was immediately obvious that no attempt had been made by the tissues of the host to adhere to it; the surrounding tissues were œdematous, bluish, and shiny. In only one instance (*Table III*, No. 10a) did the capsule adhere to the surrounding tissues (*see Fig.* 523).

Table I.—Recipient with One or Both Kidneys Intact

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1	5	6	—	220	140 80 120 80 20	1·005 1·005 1·017 1·015 1·010	
2	2	3	*B. coli*	100	125 175	1·012 1·015	
3	1	3	*Ps. pyocyanea*	87	50	1·015	
4	2	3	—	120	60 50	1·010 1·012	
5	1	2	—	105	210	1·010	
6	4	5	—	180	100 50 60 20	1·020 1·010 1·005 1·010	
7	1	2	—	170	150	1·010	
8	1	2	*Ps. pyocyanea*	110	90	1·012	
9	3	4	Negative	200	80 100 70	1·010 1·020 1·017	
10	(1) 3	4	Negative	155	58 210 200	1·010 1·012 1·015	
11	(1) 8	—	Negative	120	155 170 530 1550 2090 740 780 500	1·027 1·027 1·025 1·010 1·015 1·015 1·010 1·017	 29·5 12 53 53·5 50 54 89
12	(1) 7	8	*Staph. aureus*	140	135 100 258 400 300 125 110	1·015 1·020 1·015 1·015 1·012 1·010 1·010	
13	(1) 2	3	*Ps. pyocyanea*	225	100 50	1·015 1·010	
14	(1) 1	—	Negative	120	—50	1·010	
15	(1) 1	—	Negative	180	—50	1·015	
16	(1) 4	5	Negative	200	60 450 250 300	1·010 1·010 1·010 1·010	 20 31 40

The Physiological Behaviour of the Homotransplanted Kidney in the Neck of a Dog.—The behaviour of the homotransplanted kidney during the early phase resembles closely that of an

autotransplanted kidney (Dempster, 1950). Detailed studies of the autotransplanted kidney have provided an index of what one may expect, in the most favourable circumstances, from a homotransplanted kidney. The homotransplanted kidney is unable to concentrate sodium chloride, after salt loading, as well as the autotransplanted kidney; the maximum concentration of chloride from the homotransplanted kidney was 74 m. Eq./l., whereas that from the autotransplanted kidney was over 200 m. Eq./l. Furthermore, the daily output of urine contains a lower sodium chloride concentration; in a 24-hour specimen the homotransplant secretes a similar amount of urine as the autotransplant at a chloride concentration of 4–107 m. Eq./l., whereas the autotransplant concentrates chloride at a level of 40–170 m. Eq./l. Although large amounts of urine may be secreted by homotransplanted kidneys, the blood-urea rises steadily. The homotransplanted kidney is sensitive, during the height of a water diuresis, to minute doses of posterior pituitary extract (infundin, 0·1 m.u. intravenously). At the peak of function, the homotransplanted kidney can attain a maximum water diuretic capacity of 10 ml./min.

Holloway (1926) was under the impression that the disintegration of the homotransplanted kidney was accelerated by diuretic agents. This has not been confirmed; on the contrary, the kidneys which survived the longest were subjected to the greatest number of diuretics.

Table II.—Recipient is Bilaterally Nephrectomized

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1	1	—	—	95	150	1·035	
2	2	—	—	120	125 175	1·012 1·015	
3	3	—	—	120	150 375 275	1·010 1·020 1·015	
4	5	—	*Staph. aureus*	212	185 760 1025 1100 400	1·010 1·016 1·016 1·012 1·015	23 9·5 8·25 8·75 12
5	10	—	Negative	180	235 1760 1600 2620 2550 2300 2620 1620 900	1·022 1·016 1·015 1·015 1·015 1·015 1·015 1·015 1·020	17·5 9·5 5·5 14·25 15·5 45 52 36 23
6	10	—	Negative	190	590 1600 1620 1170 1300 1500 1400 190 70	1·020 1·015 1·018 1·018 1·010 1·015 1·015 1·015 1·105	10·75 11·75 24·25 24·25 17·3 14 18 15 10
7	2	—	*B. coli*	180	320 630	1·022 1·015	
8	4	—	*B. coli* and *Ps. pyocyanea*	115	450 880 700 400	1·017 1·012 1·012 1·010	11·5 12 8·5 7·25
9	4	—	*B. coli*	180	550 650 420 230	1·017 1·015 1·013 1·010	
10	2	—	Negative	150	50 60	1·010 1·010	
11	5	—	Negative	160	1000 2200 1450 950 800	1·012 1·010 1·020 1·017 1·018	4 8 11 7 8

Table I. Experiment I.—In *Table I* is summarized the behaviour of homotransplanted kidneys under two sets of conditions: (1) In Nos. 1–9 the homotransplanted kidneys functioned as a third kidney in the host; and (2) in Nos. 10–16 the homotransplanted kidneys functioned in dogs from which one kidney had previously been removed. It can be seen that, except in two instances (Nos. 14 and 15), all homotransplanted kidneys evoked in the host a

Table III.—Recipient received First and Second Kidney from Same Donor

No. of Dog	No. of Days secreted	Day Toxic Syndrome appeared	Organisms cultured	Weight (g.) of Kidney when removed	Daily Urine Output			No. of Dog	No. of Days secreted	Day Toxic Syndrome appeared	Organisms cultured	Weight (g.) of Kidney when removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.						Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1a	3	4	—	180	100 500 250	1·017 1·005 1·012	16 12·5 25	1b	−1	—	—	110	−50	1·010	
2a	2	—	*Ps. pyocyanea*	180	200 100	1·012 1·010		2b	−1	—	—	115	−50	1·015	
3a	3	4	—	180	214 220 98	1·020 1·015 1·017	40·5 42 49·5	3b	−1	—	—	110	−50	1·010	
4a	4	5	*Ps. pyocyanea*	240	146 360 200 165	1·010 1·015 1·010 1·012		4b	−1	—	—	190	−50	1·010	
5a	6	—	—	227	98 300 190 600 610 270	1·010 1·012 1·012 1·010 1·010 1·010	 64 66 107 73 80	5b	1·5	—	—	160	150	1·012	
6a	2	3	*Ps. pyocyanea*	200	50 30	1·012 1·010		6b	−1	—	—	90	−50	1·015	
7a	3	4	*B. coli*	190	200 300 156	1·012 1·015 1·005		7b	−1	—	—	110	−50	1·010	
8a	2	3	—	125	200 100	1·017 1·020		8b	−1	—	—	120	−50	1·012	
9a	3	—	—	150	250 300 90	1·015 1·010 1·012		9b	−1	—	—	120	−50	1·010	
10a	11	—	Negative	180	120 250 500 570 620 630 660 400 450 330 380	1·010 1·005 1·008 1·005 1·010 1·007 1·010 1·010 1·010 1·010 1·007	18 14 15 29 52 58 48 — 39 28 21	10b	1·5	—	Negative	120	200	1·012	15
11a	6	7	*Proteus vulgaris*	180	100 350 1200 700 430 70	1·010 1·015 1·005 1·008 1·005 1·005	 18 42 43 46	11b	3	—	Negative	175	1540 1400 870	1·015 1·016 1·015	4 4 11

Table IV.—RECIPIENT RECEIVED SECOND KIDNEY FROM A DIFFERENT DONOR

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output			No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.						Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1a	7	8	—	160	100 400 200 240 300 550 225	1·010 1·010 1·012 1·015 1·010 1·010 1·010		1c	5	6	*P. vulgaris*	150	280 570 180 200 150	1·022 1·010 1·010 1·015 1·012	49 49 64
2a	4	5	*B. coli*	150	50 150 260 200	1·010 1·015 1·012 1·017		2c	−1	—	—	120	−50	1·010	
3a	4	5	*B. coli*	207	100 250 120 250	1·010 1·010 1·010 1·010	24·5 28·5 84 122	3c	1·5	—	—	100	200	1·015	
4a	3	4	*B. coli*	190	100 100 100	1·010 1·010 1·020		4c	1·5	—	—	120	300	1·030	
5a	5	—	*P. vulgaris*	200	980 300 250 350	1·010 1·015 1·010 1·005	8 68 42 52	5c	4	—	*P. vulgaris*	215	60 100 200 100	1·020 1·005 1·010 1·012	
6a	4	—	Negative	150	80 300 230 350	1·015 1·020 1·015	12 13 27	6c	2	—	—	100	90 100	1·010 1·010	
7a	4	—	Negative	110	130 320 570 100	1·010 1·007 1·020	13 15 41	7c	7	—	*P. morganii*	180	450 300 1000 1000 870 870 300	1·025 1·032 1·010 1·010 1·007 1·010 1·010	34 35 46 72 38 — —

toxic syndrome at varying intervals after operation. In 11 cultures examined, 6 showed no growth, although a toxic syndrome was evoked in some instances.; 5 showed moderate growth of *B. coli*, *Ps. pyocyanea*, or *Staph. aureus*; the antibiotic used was penicillin. Previous published work claimed that a homotransplanted kidney functioning as a third kidney could lower the normal blood-urea; the results tabulated here show that a homotransplanted kidney under such circumstances does not function well or for any length of time. The average weight of a normal greyhound kidney is about 75 g.; it will be seen that the weight of a homotransplanted kidney is always increased when it has stopped functioning. This increase in weight is due both to fluid and cellular increase. A homotransplanted kidney, when the host has one of its own kidneys removed, can secrete as well as an autotransplanted kidney. All kidneys were removed as soon as the toxic syndrome became established or when the kidney had stopped secreting. Nos. 10–16, included in this group, are failures from other experiments; failures in successive transplants due to: anuria (2), arterial thrombosis (1), and vascular anomalies (3). The histological features of all kidneys will be described later.

Table II. Experiment 2.—In *Table II* is summarized the behaviour of a homotransplanted kidney in a bilaterally nephrectomized host. In no instance did a toxic syndrome occur, although organisms were grown from cultures taken from these kidneys. In 8 cultures examined, 4 showed no growth, but 4 showed growth of the same organisms listed in *Table I*; the antibiotic used was streptomycin. Water diuresis in Nos. 5, 6, 9, and 11 was normal; the maximum diuretic capacity varied from 6 ml./min. to 10 ml./min. Saline diuresis was profuse, but the concentration of chloride was low as compared with the autotransplanted kidney. It will be seen that the homotransplanted kidney usually stops secreting relatively suddenly and the arrest of function does not usually extend over a number of days.

Table III. Experiment 3.—*Table III* summarizes the behaviour of successive kidney homotransplants from the same donor to the same host. The 'first' kidney bears the letter a: the 'second' kidney has the letter b. It will be seen that the behaviour of the 'first' kidneys is as has been already indicated in the previous two tables; each host had one of its own kidneys intact when it received the 'first' kidney. The behaviour of the 'second' kidneys is very different; in 8 instances, arrest of secretion occurred within twenty-four hours; of the remaining 3, 2 secreted for thirty-six hours and 1 for three days. In all instances the period of survival of 'second' kidneys is considerably less than that of the 'first' kidneys. It is remarkable that Nos. 5a, 10a, and 11a survived the longest in this series and the corresponding 'second' kidneys also survived the longest. Nos. 10b and 11b were transplanted one week after the removal of the 'first' kidney; in all other instances the 'second' kidney was transplanted within three days of removing the 'first'. The histological features are altogether different in 'first' and 'second' kidneys. The 'first' is characterized by a cellular infiltration; the 'second' by œdema, hæmorrhage, casts, and virtually no cellular reaction. These features will be discussed in more detail later.

It was invariably the rule that 'second' kidneys started secreting immediately on opening up the carotido-jugular circulation. A small flow continued for some hours, but usually within twelve hours the flow had markedly decreased and was blood-stained, and at the end of 24 hours there was no flow whatsoever. No toxic syndrome was evoked by 'second' kidneys; nor did the host show any signs of anaphylaxis. The antibiotics used were streptomycin and terramycin, the latter being used in Nos. 10 and 11 only.

Table IV. Experiment 4.—The behaviour of a 'second' kidney from a different donor to the same host is summarized in *Table IV*; the 'first' kidney is designated by the letter a, the 'second' by c. The evidence presented here is not impressive at a first glance.

Table V.—Recipient received Second Kidney from Same Donor

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when removed	Daily Urine Output		No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when removed	Daily Urine Output	
					Volume (ml.)	Specific Gravity						Volume (ml.)	Specific Gravity
1a	1	—	—	140	450	1·010	1b	2	—	—	160	600	1·012
												600	1·012
2a	1	2	*B. coli*	170	157	1·015	2b	1	—	—	160	150	1·012
3a	1	—	Negative	140	50	1·010	3b	1	—	—	125	50	1·012
4a	1	—	Negative	250	280	1·010	4b	3	—	—	180	150	1·010
												700	1·020
												950	1·022
5a	1	—	—	130	50	1·010	5b	3	—	—	180	150	1·010
												850	1·020
												250	1·020
6a	1	—	Negative	120	100	1·010	6b	1	—	—	110	50	1·012

Theoretically, a 'second' kidney should secrete for the average length of time of a 'first' kidney. In only 4 instances is this the case; in 2 instances (Nos. 2c and 4c) the kidney became anuric after twenty-four hours

and in one instance (No. 3c) the host died twenty-four hours after operation but the kidney secreted well. The two cases of anuria after twenty-four hours show the histological features typical of what will be described later as the 'anuric kidney'. On the other hand, the 4 instances in which the 'second' kidney secreted for the average length of time of a 'first' kidney (and in 1 instance, No. 7c, for longer than the 'first'), is positive evidence against an immunity having been developed which was immediately involved against the kidney from another donor. The kidney of No. 5c was removed because the dog was vomiting; post-mortem showed that the dog had developed intussusception. No 'second' kidney in this experiment showed the features typical in any way of 'second' kidneys in Experiment 3. Thus, there is no evidence that kidneys from different donors share the same antigens; the evidence points in favour of an individual specificity of tissue antigen. The antibiotic used was streptomycin.

Table VI.—THE KIDNEY WAS IRRADIATED IN DONOR BEFORE TRANSPLANTATION

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1	2	—	Negative	120	100 150	1·010 1·010	
2	7	—	Negative	180	330 180 600 880 520 100	1·005 1·007 1·005 1·006 1·007 1·010	19 11·5 13 6·5 5·5 10
3	4	—	*P. morganii*	120	340 500 700 500	1·022 1·022 1·012 1·010	39 8
4	4	—		120	200 310 470 320	1·010 1·010 1·010 1·010	
5	9	—	Negative	180	400 470 500 950 860 660 800 600 280	1·005 1·002 1·005 1·005 1·002 1·002 1·003 1·003 1·002	10 12·5 8 11 10 16 16 13 11
6	2	3	*P. morganii*	200	400 400	1·007 1·000	3 9

Table V. Experiment 5.—In this experiment, all 'first' kidneys were removed on the second day, usually because of anuria; the 'second' kidney was transplanted four days later. All the 'second' kidneys in this experiment show the typical features of 'first' kidneys in the previous experiments. The evidence presented in *Table V* shows: (1) A period longer than twenty-four hours i

Table VII.—THE HOST WAS IRRADIATED 24 HOURS BEFORE RECEIVING THE KIDNEY

No. of Dog	No. of Days Secreted	Day Toxic Syndrome Appeared	Organisms Cultured	Weight (g.) of Kidney when Removed	Daily Urine Output		
					Volume (ml.)	Specific Gravity	Concentration of Chloride m.Eq./l.
1	3*	—	Negative	120	200 350 300	1·010 1·015 1·010	30 23 20
2	1†	—	Negative	130	150	1·010	10
3	4	—	Negative	80	300 450 480 300	1·012 1·015 1·005 1·015	15 23 19 24
4	6	—	Negative	125	240 300 400 430 380 200	1·010 1·005 1·016 1·012 1·015 1·018	15 14 11 18 16 23

* Removed while still secreting. † Died after 24 hours.

required by the host to produce antibody against a homotransplanted kidney: this is some evidence against naturally occurring antibodies. (2) The anuria encountered so frequently in homotransplanted kidneys is not necessarily of immunological significance. The antibiotic used was streptomycin.

Table VI. Experiment 6.—In this experiment, the kidneys of the future donor were irradiated twenty-four hours before transplantation. *Table VI* shows the behaviour of such irradiated kidneys in bilaterally nephrectomized hosts. The length of survival corresponds to that found in other experiments. The aim of this experiment was to block the activity of the reticulo-endothelial system of the kidney. Nos. 1–3 stopped secreting with virtually no evidence of a plasma-cell reaction; Nos. 4 and 5 showed a few focal areas of plasma cells—presumably areas not adequately irradiated; No. 6 became infected and stopped secreting on the third day and the only cells seen were polymorphs. In none of the sections was it obvious that the endothelial cells were swollen or differentiating, as seen in *Fig.* 513. The results of this experiment add further evidence to the fact that the plasma-cell infiltration which accompanies the disintegration of homotransplanted kidneys is renal in origin. The results also show that some mechanism other than a cellular infiltration brings about the disintegration of homotransplanted kidneys. The antibiotic used was terramycin.

Table VII. Experiment 7.—In this experiment the host received total body irradiation twenty-four hours before the operation; at the operation the host was bilaterally nephrectomized. Except for No. 2, whose host died twenty-four hours after the operation, all kidneys show a plasma-cell infiltration of equal intensity to those in previous experiments 1–5. No. 1 was removed while still functioning well, for histological control; already by the third day an advanced plasma-cell infiltration was obvious. The fact that the kidneys did not survive any longer than those in other groups may mean that the dosage of irradiation may not have been sufficient to prevent antibody production; further experiments are in progress. On the other hand, the plasma-cell infiltration, autochthonous in origin as it is, may be a contributory factor in arresting secretion. The antibiotic used was streptomycin.

Experiment 8.—Three dogs, which had already each received a kidney from other dogs, had blood drawn off four days after the removal of the 'first' disintegrating homotransplanted kidney. The blood was allowed to settle and then the serum (usually amounting to about 150 ml.) was injected into the original donor of the kidney. After one week, the urine of each original donor was examined for albumin; the donors were then killed and the remaining kidney was examined histologically. No pathological feature was found.

If the host had developed anti-kidney antibodies to the homotransplanted kidney, theoretically the serum should now contain toxic factors against the remaining kidney of the donor. There are several possibilities which could explain the failure to produce any renal lesions with homologous serum:—

1. There may have been no anti-kidney antibodies circulating in the host when the blood was drawn off.
2. Any antibodies present in the serum of the host may have been in low titre and not potent enough to produce any toxic effect; Smadel (1936) and Halpern, Tolliet, and Martin (1949) (these latter review the work of Masugi's paper to date) showed that the gravity of experimental nephritis (using heterologous serum) depended on the quantity of antibody injected.
3. The liver and lungs of the dogs may have mopped up a great deal of anti-kidney antibodies and so reduced the potency of the serum. Masugi found that the severest lesions were produced when the anti-kidney serum was injected straight into the renal artery.

FIG. 511.—Photograph of a nephro-arteriogram of an autotransplanted kidney functioning well. Shows marked cortical concentration of pyelosil.

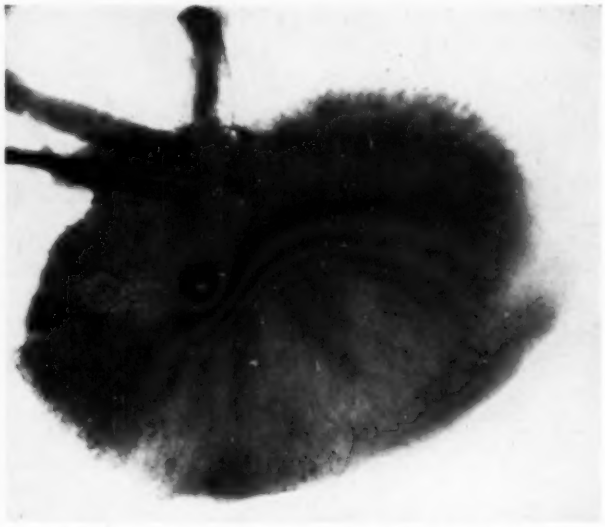

FIG. 512.—Photograph of a nephro-arteriogram of a homotransplanted kidney which stopped secreting on the eighth day. There is no cortical concentration of the injected pyelosil.

Nephro-arteriograms.—On screening, the injected pyelosil was seen to enter quickly the autotransplanted kidney and to concentrate in the cortex (*Fig.* 511). This was not the case with the disintegrating homotransplanted kidney. In the latter the opaque fluid could be seen entering the interlobar and interlobular arteries, but no concentration in the cortex was observed (*Fig.* 512). Serial photographs confirmed this finding.

Histological Features of 'First' Kidneys.—The outstanding feature is a cellular infiltration which will be described in detail in the next section.

Cortex: The cellular infiltration starts in the cortex and at any given stage is always more advanced there. The glomeruli are relatively bloodless and

some are in complete spasm with no signs of patent capillaries. There is no cellular change either in the endothelium or epithelium of the tufts. The basement membrane of the dog's glomerulus is rather thicker than in the human; usually this basement membrane appears even more thickened. The proximal tubules appear quite normal until the late stages. The brush border begins to fade about the third day after operation and is barely visible, and is usually completely absent by the seventh day. In the late stages casts are visible in the lumina and droplet degeneration is obvious in the tubular cells. The distal tubules usually show signs of back-pressure; there is usually some dilatation. In the late stages the cells show droplet degeneration and often vacuolation.

Medulla: Usually free from cellular infiltration. The collecting tubules show droplet degeneration in the late stages.

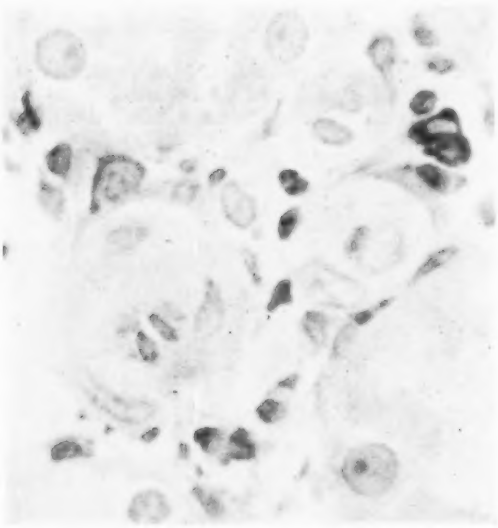

FIG. 513.—Biopsy from a 'first' homotransplanted kidney on the third day. This shows the early stage of the perivascular plasma-cell infiltration. At this stage most of the cells are typical 'transitional' cells of Fagraeus. Note also that the vascular endothelium of three arterioles is swollen and pyronin-positive. It is suggested that the 'transitional' cells are derived, in part, from the differentiating vascular endothelial cells. (Methyl green pyronin orange.) (× 880.)

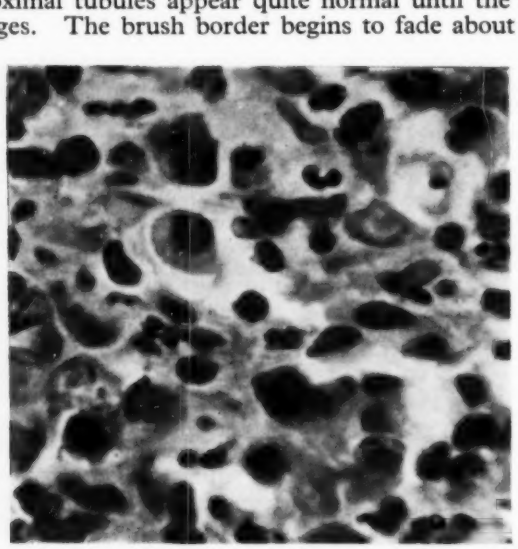

FIG. 515.—Section from a 'first' homotransplanted kidney removed on the seventh day. The cellular infiltration consists of plasma cells and polymorphs; the pear-shaped cell about centre is probably an effete plasma cell. (Methyl green pyronin orange G.) (× 760.)

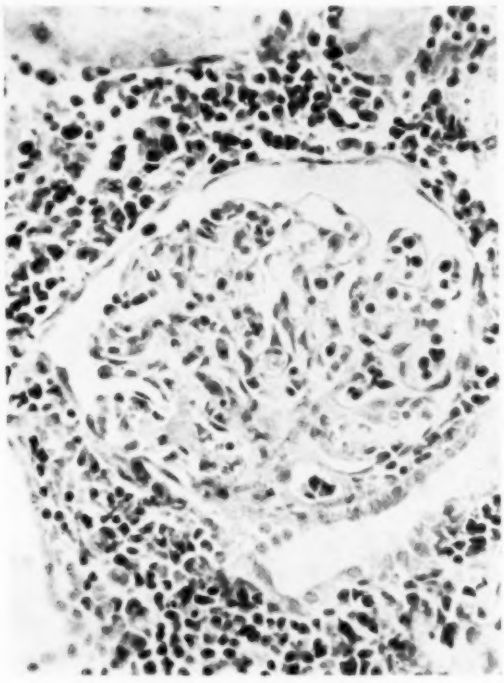

FIG. 514.—Section from a 'first' homotransplanted kidney removed on the ninth day after a period of good secretion. Mature plasma cells can be seen infiltrating the kidney and are particularly concentrated around the glomeruli. (Methyl green pyronin orange G.) (× 268.)

Sinus renalis fat: A mild plasma-cell infiltration can be seen in the late stages. The vascular endothelium is swollen and pyronin-positive.

Capsule: Thickens rapidly both in collagen and cellular content (*see Fig.* 523). The cells are similar in type to those seen in the renal interstitium. The capillary endothelium is pyronin-positive.

Renal artery: Shows no sign of disintegration at the site of anastomosis with the carotid artery of the host nor any signs of spasms. The endothelium is *not swollen* and *not pyronin-positive*. Healing continues at the anastomosis at a time when the kidney is disintegrating. No cellular infiltration occurs in its wall. The vascular endothelium of the intrarenal branches of the renal artery is swollen and strongly pyronin-positive.

Ureter: Swells rapidly, as has been described for the autotransplanted kidney (Dempster, 1950). A cellular infiltration occurs in the submucosal and adventitial coats. The vascular endothelium is swollen and pyronin-positive.

The Cellular Infiltration in 'First' Kidneys.—The degree of cellular infiltration varies and in some instances is slight before the immune reaction arrests the function of the homotransplanted kidney. Usually, however, some time between the second and third day after transplantation, an immature plasma-cell reaction commences (*Fig.* 513). Initially, this reaction is around the small blood-vessels and particularly around the afferent arterioles and intertubular

capillaries; later the cells are to be found everywhere in the cortex and are then mainly mature plasma cells (*Figs.* 514, 515). Even at this stage there is virtually no cellular infiltration in the medulla,

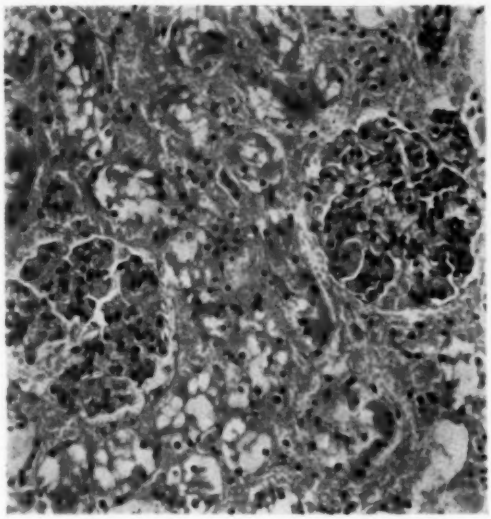

FIG. 516.—A photomicrograph of a 'second' homotransplanted kidney (same donor, same recipient—*see Experiment* 3) removed twelve hours after transplantation. This section shows the *initial* '*hyperæmia*' which occurs in such kidneys.; this really is a picture of statis of red cells. (H. and E.) (× 152.)

although the medullary vascular endothelium is pyronin-positive.

In the late stages, in addition to the mature plasma cells, polymorphs enter and complicate the picture (*Fig.* 515). These polymorphs enter probably to deal with dying renal parenchyma; bacterial

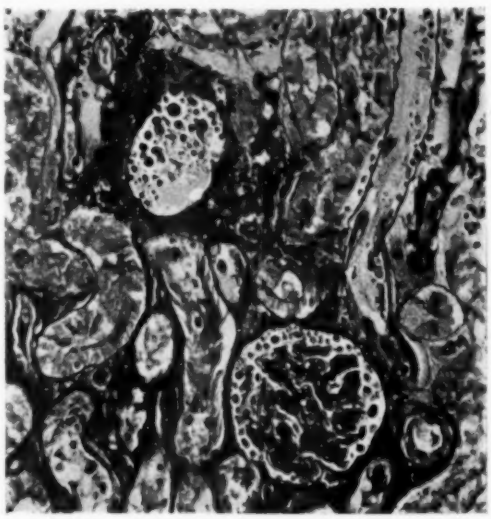

FIG. 518.—A photomicrograph of a 'second' homotransplanted kidney (*Experiment* 3) removed after twenty-four hours. (× 140.)

colonization is frequent at this stage and leads to necrosis of the renal parenchyma. There was no evidence of lymphocytes developing into plasma cells. The cells as seen in *Fig.* 513 are not dividing but actively differentiating cells; it will be suggested later that these cells are renal in origin.

Histological Features of 'Second' Kidneys.—Within twenty-four hours, usually, the 'second' kidney has stopped secreting; there is massive death of most nephrons in the kidney. Tubular

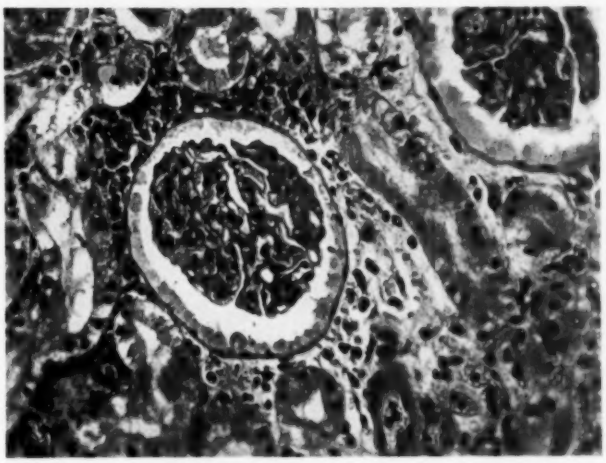

FIG. 517.—Section from a 'second' homotransplanted kidney removed thirty-six hours after operation. Shows tuft capillary spasm, subcapsular precipitate, œdema, and tubulorhexis; a plasma-cell infiltration can be seen. (H. and E.) (× 192·5.)

damage is the most marked; every lumen is filled with cast material and the cells are swollen, degenerate and the nuclei are pyknotic, but the brush border is visible. The degeneration of the tubules takes the form of hyaline droplet degeneration. Throughout the kidney there is marked interstitial œdema and free hæmorrhage. Occasionally mitosis of a tubule cell can be seen. The state of the glomeruli varies; there is a protein precipitate of varying

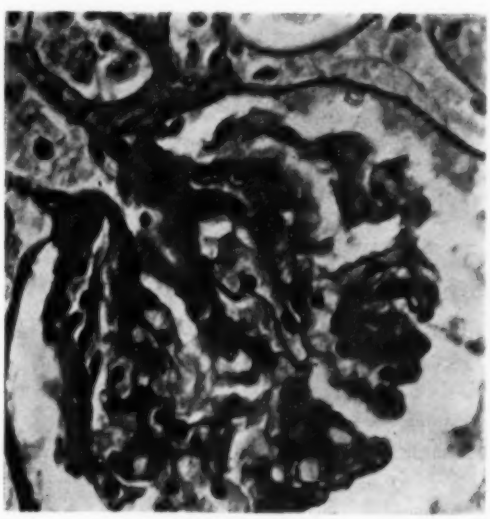

FIG. 519.—Section taken from a 'second' homotransplanted kidney twenty-four hours after operation. Shows complete capillary spasm and intense fibrinoid deposit. (Allochrome.) (× 440.)

intensity in the subcapsular space which sometimes contains epithelial nuclei (*Figs.* 516–518). The precipitate is either in the form of globules or amorphous masses; this precipitate is probably filtered protein, but occasionally one can see a portion of proximal tubules together with its brush

border in the subcapsular space which suggests regurgitation.

The tufts vary in their blood content. They usually are relatively bloodless; the basement membrane is thickened and swollen; in severe cases there are usually varying amounts of what appears to be fibrinoid which may be due to serum being forced into the capillary walls (*Fig.* 519). In those cases where a 'second' kidney has survived longer than twenty-four hours or has been left in the host for a

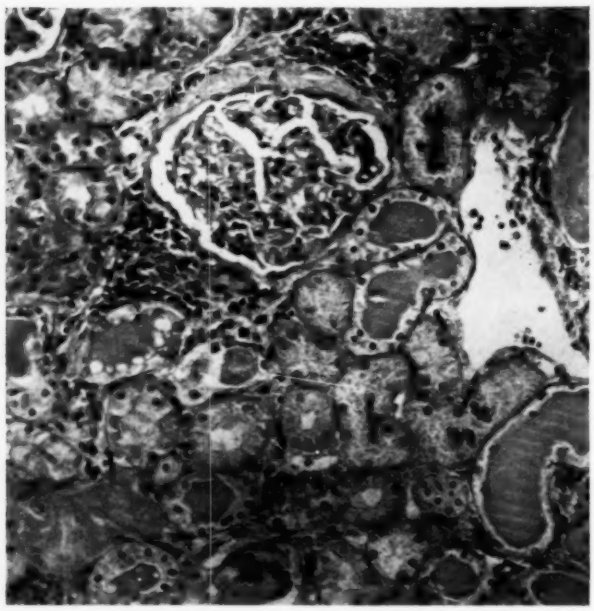

FIG. 520.—Section from an 'anuric kidney' forty-eight hours after operation. Shows widespread tubular damage; the cells of some tubules show syncytial formation. (H. and E.) (× 155.)

further period, a cellular infiltration around the glomeruli is to be found (*Fig.* 516).

These features suggest a hypersensitivity reaction, but as the factors involved are unknown, the use of this term is not justifiable; the increased capillary permeability (most marked in *Fig.* 518) is probably due to a quantitative change in the antigen-antibody reaction presumed to take place in 'first' kidneys. The over-all picture can be explained on the basis of acute inflammation and its associated phenomena.

The 'Anuric Kidney'.—A 5 per cent incidence of anuria was found in autotransplanted kidneys. (Dempster, 1950). The anuria is usually evident from the beginning. Although an apparently good circulation occurs through the kidney, no urine is secreted. The glomerular tufts are usually enlarged and swollen. There is no precipitate in the subcapsular space. All the tubules are uniformly desquamated and the cells show a syncytial appearance; casts are to be seen in the lumina (*Fig.* 520). There are seldom any signs of fibrinoid deposit in the tuft capillaries; this is an important point in differentiating this condition from the histology of the 'second' kidney.

The cause has not been determined. It may be due to renal nerve stimulation producing capillary spasm during the mobilization of the kidney in the donor. Although the incidence in homotransplanted kidneys of this type of anuria was 16 per cent, no immunological significance can be drawn from this phenomenon, which constitutes the most important technical problem in transplanting kidneys. It must be differentiated from the appearance seen in 'second' kidneys; it should be left out of immunological considerations as some physiological rather than immunological factor is at play.

DISCUSSION

A Consideration of Infection in Relation to the Cellular Infiltration and Arrest of Function of Homotransplanted Kidneys.—Wu and Mann (1934) concluded their histological findings with the impression that "the pathologic picture probably represents pyelonephritis from an ascending infection of the urinary tract". Williamson (1923, 1926) found that in his experiments abscesses were rarely seen in the cortex of homotransplanted kidneys. This is not confirmed by the present experiments. Williamson (1926) concluded: "An ascending infection, so far as I have been able to determine from my studies, does not begin until the physiologic changes in the transplant begin to impair and diminish the urinary output." Williamson envisaged the following series of events leading to the disintegration: an acute atypical glomerulonephritis, acute general nephritis, and an ascending pyelonephritis. No feature in common with glomerulonephritis has been found in the present experiments.

In this series of 85 homotransplanted kidneys there was some evidence that an ascending infection could have taken place in 16 per cent (*Fig.* 521); in these instances, however, there existed a cortical cellular infiltration of a more advanced nature than that in the medulla. In the remainder of this series (84 per cent) the medulla was virtually clear of any signs of a cellular infiltration (*Fig.* 522). Therefore, no support can be given to Williamson (1926) or to Wu and Mann (1934) that the cellular infiltration represents the end-results of an ascending pyelonephritis.

The question of a possible blood-borne infection must now be considered. Autotransplanted kidneys removed many weeks after operation show no evidence of dilated tubules (*see Fig.* 510). Virtually without exception, all homotransplanted kidneys showed varying degrees of dilated tubules within a few days of operation; Smadel (1936) comments on this finding in experimental glomerulonephritis. It is difficult to explain this finding, but, in itself, it is sufficient explanation of the marked susceptibility to infection of the homotransplanted kidney. Slight degrees of hydronephrosis will slow down the renal circulation and favour the localization of bacteria which normally would traverse the renal vasculature; the normal kidney has virtually no power to localize or excrete bacteria carried to it by the blood-stream (De Navasquez, 1950, has reviewed this subject). The bacteria which were cultured from disintegrating homotransplanted kidneys most likely entered by the blood-stream. The exact point in time is sometimes difficult to determine. It is obvious that there are varying degrees of incompatibility and hence varying periods of survival of homotransplanted kidneys. Thus, homotransplanted kidneys removed at a relatively early stage after operation and showing signs of bacterial colonization, need not necessarily be

regarded as failures due to infection; the bacterial localization could quite well have developed after the critical phase when the homotransplanted kidney is overcome by the immune reaction of the host. The polymorph infiltration which comes to complicate the plasma-cell infiltration, need not necessarily signify infection; polymorphs are attracted very quickly to any area undergoing death.

Acute interstitial nephritis in the human is unique in that in the initial stages of an acute renal infection a cellular infiltration occurs mainly composed of plasma cells. This is a rare condition. However, it should be borne in mind that plasma cells can appear in acute inflammatory lesions in the kidney.

FIG. 521.—Section of a 'first' homotransplanted kidney showing areas of cellular infiltration in the medulla; the infiltration is more advanced in the cortex. (H. and E.) (× 3.)

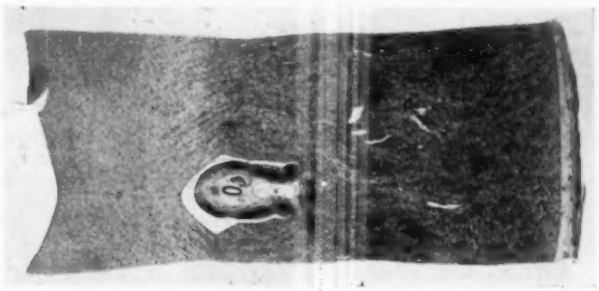

FIG. 522.– Section of a 'first' homotransplanted kidney showing the cellular infiltration confined entirely to the cortex. (H. and E.) (× 2·5.)

As regards canine nephritis: there is no evidence that any of the known types of nephritis are responsible for the plasma-cell infiltration already described. Signs of past infection can sometimes be seen in the greyhound kidney; such sections have to be left out of any consideration of the nature of the disintegration of the homotransplanted kidney. One is forced to reduce the material for analysis to those kidneys which show no signs of past nephritis and are little complicated by a polymorph infiltration.

The Significance of the Plasma-cell Infiltration.—The general features which have been described correspond to those found in the experiments conducted by Bjorneboe and Gormsen (1943) in relation to plasma-cell reactions in the kidneys of hyperimmunized rabbits. These authors were quite convinced of the autochthonous origin of the plasma cells; they envisaged the development of the plasma cells from the reticulum cell and from the histiocyte in the reticulum cell-free renal sinus fat. Such an origin of plasma cells is quite compatible with the findings in the present investigation. However, in view of the pyronin-positive character of the vascular endothelium (*see Fig.* 513), it is possible that vascular endothelial cells as well are differentiating into plasma cells. This feature was suggested to me by Dr. D. Trevan, who has found similar findings in the capillary endothelium surrounding areas of injected toxoid in rabbits. Another source of plasma cells has been suggested by Block (1952), who found evidence that in bone-marrow plasma cells develop from the perivascular mesenchymal cells of the arterial capillaries distal to the termination of the smooth-muscle coat. Thus, contrary to what Loeb and others have shown with implanted tissues, the disintegration of a homotransplanted kidney is accompanied by a cellular reaction which is renal in origin. But what is the significance of these cells differentiating into plasma cells? The results of *Experiment* 6 suggest that the absence of the plasma cells in the homotransplanted kidney in no way prolongs the life of the homotransplanted kidney. The plasma cells may be produced in response to local tissue damage; if this is the case, the plasma cells are not a response against the host. But if the plasma cells appear due to direct stimulation by the host blood, and these plasma cells are concerned in the synthesis of nucleic acids (suggested by the intense pyronin-staining of the cytoplasm) and hence antibody production, it is possible that the antibody is being liberated locally and this may have a toxic effect on the kidney.

That the plasma cells are not wandering from the host tissues can be seen in *Figs.* 523 and 524. On the other hand, the cellular infiltration in *Fig.* 523 shows no tendency to wander into the host tissues. Thus, contrary to what Loeb found with implanted tissues, no cellular reaction is developed by the host around homotransplanted tissue. This suggests, then, that if the host is responsible for the disintegration of homotransplanted kidneys, a humoral mechanism is at play.

The Nature of the Humoral Process.—The results of the experiments show that an immunity takes some time to develop. The results of *Experiments* 3 and 4 show that the immunity developed is individually specific. The delay in the disintegration of a 'first' kidney excludes naturally occurring antibodies in the host as being the factors involved. The rapid disintegration of 'second' kidneys suggests a process akin to an actively acquired immunity having been developed. Of course, it can only be inferred from the evidence presented here that antibodies are involved. It is inferred that circulating antibodies localize in the kidney and lead to arrest of filtration; this process is not connected with a blood-stained urine in 'first' kidneys. The fact that 'second' kidneys (*Experiment* 3) seldom secrete for more than a few hours suggests: (1) that circulating antibodies are still present after the removal of 'first' kidneys; or (2) that antibodies develop rapidly and with increasing potency after the transplantation of the 'second' kidney.

A Consideration of Experimental Nephritis in Relation to the Disintegration of Homotransplanted Kidneys.—Lippman, Marti, and Campbell (1952, a) have recently reviewed all previous work on the experimental production of nephritis. It is difficult to correlate the vast experimental

data with what is known as glomerulonephritis in the human; in this disease, it has been suggested, auto-antibodies are the cause of the lesion. Kay's (1940) attitude to the Masugi theory of 'reverse anaphylaxis' has been neglected; Kay (Kay, 1940; Kay, Lucchesi, and Rutherford, 1941) suggested that the rabbit formed antibodies against the injected duck serum which was antigenic to the rabbit; the union of these antibodies and antigens in the kidney produced the lesion. Kay (1940) was able to prevent the development of nephritis by irradiating the rabbits previous to the injection of the nephrotoxic serum. However, it is not easy to reconcile this concept with the fact that fatal lesions can be produced in eight hours, depending on the amount of antibody in the nephrotoxic serum (Lippman and others, 1952, a).

The introduction of homologous anti-kidney serum does not produce nephritis; *Experiment* 8 however, does not necessarily confirm this. Cavelti and Cavelti (1945) claimed that homologous anti-kidney serum required the presence of streptococci before a nephritis could be induced; this finding was not confirmed by Humphrey (1948) or by McKee and Swineford (1951). None of this work sheds any light on the processes involved in the disintegration of the homotransplanted kidney. Recent work, however, suggests certain possibilities.

The aim of recent research on serum nephritis has been to demonstrate the antigenic element in kidney tissue (Solomon, Cardella, Fanger, Dethier, and Ferrebees, 1949; Greenspon and Krakower, 1950; and Krakower and Greenspon, 1951; the last contains a review of this development). It was first of all shown that the antigen resided in the cortex of the kidney; then Pressman, Eisen, Siegel, Fitzgerald, Sherman, and Silverstein (1950) showed that anti-kidney antibodies localized in the glomerulus; Solomon and others (1949) showed that the potency of nephrotoxic serum could be nullified by absorbing it with a suspension of isolated glomeruli; recently Krakower and Greenspon (1951) have shown, convincingly, that the basement membrane, alone of all the elements of the kidney, is antigenic.

There is evidence that the basement membrane of homotransplanted kidneys is morphologically changed in that it is thickened and more prominent; this is particularly so in 'second' kidneys (*Fig.* 51[illegible]). The glomerular tufts are relatively bloodless and their contraction may be associated with changes in the basement membrane. According to McManus (1948) the endothelium of the tuft capillaries is not continuous and no endothelial basement exists; Jones (1951) and others maintain that there are two basement membranes. In any case, the tuft capillaries and basement membrane are so closely applied to one another that it is difficult to envisage damage in one without some change in the other. Pressman, Sherman, and Korngold (1951) suggest that as the uptake of injected anti-kidney localizing antibodies is so rapid, the uptake must take place on the vascular endothelium of the kidney and particularly in the tuft; the tuft is the most vulnerable part of the renal vasculature. Thus they suggest that the blood-vessels are both antigenic and antibody-fixing.

Chikamitsu (1940) came to the conclusion, from his studies on the production of glomerulonephritis by anti-lung and anti-kidney sera, that small blood-vessels generally are antigenic. Eisen, Sherman, and Pressman (1950) also were of the opinion that there were substances in lung and kidney which were antigenically similar. These authors point, as further confirmatory evidence of this, to the work of Seegal and Loeb (1946) and Smadel (1936); the former produced glomerulonephritis in rats by anti-rat placenta rabbit serum; and the latter author showed that a liver homogenate contained the nephrotoxic factor of anti-kidney serum.

If this is true, the concept may be taken a step further: the small blood-vessels of the homotransplanted kidney are not only antigenic and antibody-fixing (i.e., the antibodies of the host), but are also capable of producing antibodies against the

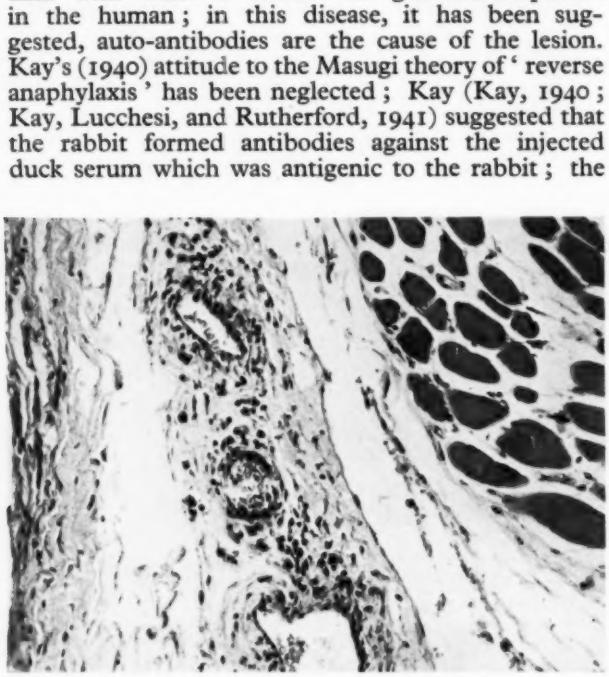

FIG. 523.—Section of the capsule of a 'first' homotransplanted kidney adherent to the local host muscle. The cellular infiltration consists of immature plasma cells, is capsular in origin and there is no evidence of cells invading from the host. (H. and E.) (× 192·5.)

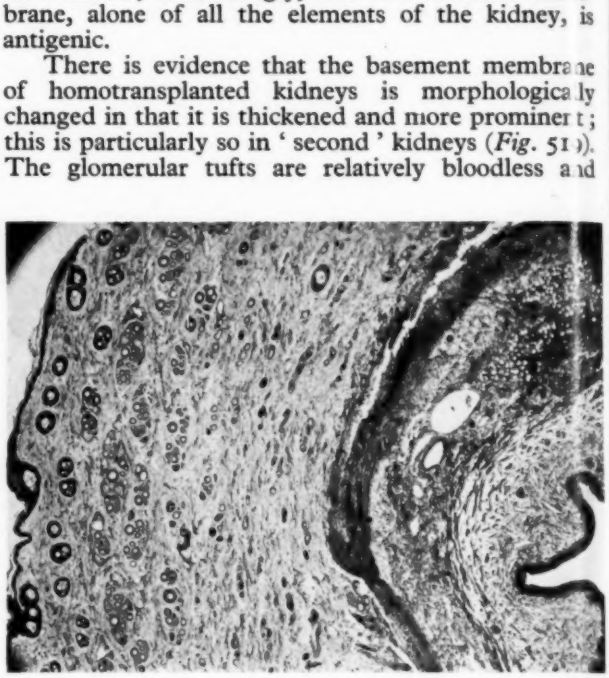

FIG. 524.—Section of the ureter of a 'first' homotransplanted kidney as it emerges on the skin surface of the neck of the dog. Although there is a cellular infiltration in the wall of the ureter, there are no cells infiltrating from the host tissues, which are separated from the ureter by a wall of fibrin and red cells. (H. and E.) (× 15.)

host. The basis for this last suggestion has been laid in the section dealing with the significance of the plasma-cell reaction and pyronin-staining nature of the renal vascula-endothelium. Such a concept would help to explain the histological findings in the disintegrating homotransplanted kidney. At the same time, this concept does not fit the changes occurring in experimental nephritis or glomerulonephritis in humans. In these diseases, presumably due to an antigen-antibody reaction, the first changes occur in the tuft endothelial cells and then in the capsular epithelial cells—both of which proliferate markedly; any change in the basement membrane is insignificant in the early stage.

Sarre and Wirtz (1939) and Lippman and others (1952, a) have demonstrated the rapid uptake of injected anti-kidney globulin by the kidney; the latter claim that the damage is done instantly. A homotransplanted kidney actually connected to the circulation of the host will be subject, sooner or later, to constant bombardment by host antibodies; this will continue until irreparable damage is done. Lippman and others (1952, a) have postulated that after the vascular bed is fully saturated with host antibodies, the tubule cells may then fix circulating antibody. Lippman, Cameron, and Campbell (1950) have demonstrated that renal tubule cells in tissue culture can be damaged by nephrotoxic serum. But the recent attempt by Lippman, Marti, and Jacobs (1952, b) to prove that nephrotoxic serum does not produce tubular ischæmia is not satisfactory. The initial hyperæmia found in their experiments and found in the present experiments (*Fig.* 516) to be merely stasis was not correlated with later developments, which usually involve intense tuft spasm (*Fig.* 519). There is sufficient evidence in 'second' kidneys to show that the tubulorhexis is due to ischæmia alone and not to direct toxic action on the tubule cells.

The Cause of Arrest of Function of the Homotransplanted Kidney.—The homotransplanted kidney usually stops secreting quite suddenly. It is obvious on exploring a homotransplanted kidney which has stopped secreting that the blood-flow through the kidney is diminished; the pulsations in the renal artery are very feeble; the kidney takes a long time to distend when its vein is clamped; a kidney in this condition is not, however, cyanosed—it remains red. The nephro-arteriograms (*Fig.* 512) show that the cortical circulation is definitely abnormal. In the past, the following suggestions have been put forward to explain arrest of function:—

1. *Arterial thrombosis*: Wu and Mann (1934) found a higher incidence of renal artery thrombosis in homo- than in autotransplanted kidney. This has not been confirmed; the incidence has been under 2 per cent.

2. *Diuretics*: Holloway (1926) was under the impression that diuretics accelerated the disintegration. This has not been confirmed.

3. *Constriction by capsular thickening*: Wu and Mann (1934) considered that the hypertrophy of the capsule acted as a constricting agent to the renal circulation. There is no doubt that marked thickening of the capsule does occur (*Fig.* 523), but an even greater thickening occurs in the autotransplanted kidney; in fact, the evidence is that a new subsidiary circulation develops between the tissues in the neck and the autotransplanted kidney.

4. *Infection*: There is no evidence that infection is the fundamental factor; however, it is conceded that infection does accelerate necrosis of an already altered renal parenchyma.

5. *Vascular spasm*: The nephro-arteriograms show reduced cortical circulation. It is possible that after the initial capillary dilatation (*Fig.* 516) a generalized vascular spasm occurs which is particularly reflected in the tuft capillaries—always the most vulnerable part of the renal vasculature; and that this spasm is a manifestation of the antigen-antibody reaction in the homotransplanted kidney. When the blood-flow through the tufts is reduced, filtration will cease, and this is sufficient explanation of the sudden arrest of secretion. In addition, the swelling and differentiation of the vascular endothelial cells must contribute to the slowing down of the renal circulation (*Fig.* 513). The widespread tubular damage could be explained by the tuft capillary spasm. Thus the viability of the whole kidney is reduced and at this stage polymorphs and bacteria infiltrate and hasten the disintegration. This concept conforms to recent principles advocated by Oliver, MacDowell, and Tracy (1951).

Tissue Adaptation.—Loeb (1945) distinguishes between two types of adaptation within an organism: (1) An adaptation depending on a biochemical harmony of all tissues in the body; this is the 'essential individuality' and is ultimately genetic in origin. (2) An adaptation presented by the normal interaction of the various organs and parts of organs within an organism; this is the 'mosaic individuality'.

So long as it functions, the homotransplanted kidney fits into the second or 'mosaic' adaptation within its host. The foreign kidney functions in as responsible a manner as the autotransplanted kidney in the neck of a dog; it reabsorbs water and electrolytes, responds to hormone influence, and if the host is given a water load the homotransplanted kidney responds with a diuresis. But this 'mosaic' adaptation is short-lived because the 'essential' adaptation never takes place and so complete rejection by the host results. This rejection is due to an actively acquired immunity on the part of the host; and this is as far as the researches of Medawar take us. But this is not the whole story so far as the homotransplanted kidney is concerned.

The Host-homotransplant Relationship.—The homotransplanted kidney contains a reticulo-endothelial system which is just as sensitive as that of the host; even before the host has developed antibodies against the kidney, the reticulo-endothelial cells of the latter have begun to swell up and to differentiate into plasma cells. This plasma-cell reaction may signify antibody formation against the host. The concept of such an interplay of forces leading to the destruction of a homotransplanted organ is not to be found in Loeb's arguments. Two reticulo-endothelial systems pitted against one another in the circulation of the same organism is a biologically unique phenomenon.

A homotransplanted organ connected to the circulation of the host is a biological entity never adequately faced up to by Loeb, who rather weakens

his case for a local immunity with the following remarks: "Moreover, the individuality differential substances produced in the transplant, instead of diffusing into the adjoining area, have a chance to be carried directly into the general circulation of the host, where they are much diluted. It may therefore be expected that the local reaction around the transplant, which is so prominent a feature in the ordinary kind of transplantation, is lacking around transplants which are joined to the host by means of blood-vessels." (Loeb, 1945.) The present experiments confirm this expectation, which, of course, implies a systemic humoral mechanism at work and not a local tissue immunity. The host-transplant interaction will not be evident if implantation techniques are employed. The results of implantation, whatever their significance, are of no value in demonstrating the real dynamics of the disintegrative process in homotransplanted organs. In fact, the evidence in the present experiments is such as to allow one only to infer that the host destroys the homotransplant by means of an antigen-antibody reaction. But the evidence of how the homotransplanted kidney reacts to its new environment strongly suggests antibody formation against the host.

The Host Reaction.—In an organ such as the homotransplanted kidney anastomosed to the host's circulation, there is no good reason why an immune reaction by the host should manifest itself by a cell reaction in the kidney. Antibodies, transported in the serum of the host, could be liberated on the vascular endothelium of the kidney; there is strong evidence from studies in experimental nephritis that antibodies are liberated on the capillary endothelium and have no time to diffuse into the interstitial tissues (Pressman and Sherman, 1951, a, b). However, this concept applies to injected antibodies; it is certainly conceivable that the serum of the host will circulate in the interstitium of the homotransplanted kidney. Even so, a cellular infiltration in the early stages, especially as it is made up of differentiating cells (*Fig.* 513), is much more likely to be of renal origin; but later, presumably in response to dying tissue, polymorphs enter the kidney from the host circulation and accelerate the necrosis in a previously altered renal parenchyma. The local tissues of the host take no part in rejecting the homotransplant; one must conclude that the process of rejection of a homotransplanted kidney is mediated by a humoral mechanism.

The Price of Over-specialization.—It is well known that the higher in the phylogenetic scale an animal is, the more highly developed is its ability to form antibodies; the price of this evolutionary overspecialization in dealing with foreign material is a crude, indiscriminating, and blind individualism. Homotransplantation of organs is not effected in nature (although the homotransplantation of a sperm is an everyday occurrence); thus, an animal presented with a foreign organ connected to its circulation has no evolutionary experience to guide it in its attitude to that organ. Its reticulo-endothelial system rejects all foreign matter in a similar manner, and the result is complete rejection as if the life-saving organ were of no more importance to survival than a microbe. We are just on the fringe of our knowledge of the nature of the processes involved in the rejection of homotransplanted tissues; for fuller knowledge of these processes one should try to homotransplant organs in their natural conditions as far as possible; it is surely obvious that implanting pieces of tissue in the lower animals is not a profitable approach to the problem.

SUMMARY

1. An analysis of the behaviour of 85 homotransplanted kidneys is given.

2. The theory of local tissue immunity (Loeb) is discussed and reasons given for its rejection. Evidence is presented which suggests that homotransplanted kidneys are rejected by means of an actively acquired immunity in the host.

3. The plasma-cell infiltration which accompanies the disintegration of homotransplanted kidneys is shown to be renal in origin; no local cell infiltration occurs between host and homotransplant.

4. The part played by infection in the disintegration of homotransplanted kidneys is discussed; the relationship of the findings of experimental nephritis to homotransplant disintegration is analysed.

5. The significance of the plasma-cell infiltration is interpreted either as a local reaction against altered renal tissue or as an attempt at antibody formation against the host; the later is the more likely interpretation.

6. The possible causes of the arrest of function are discussed and all rejected except vascular spasm.

7. The possible origin of plasma cells infiltrating the kidney from renal vascular endothelium is tentatively put forward.

8. The host–homotransplant relationship is stressed. The host reacts against the kidney and the latter against its host.

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METASTASIZING HÆMANGIOMATA

A CASE OF MALIGNANT HÆMANGIO-ENDOTHELIOMA

BY DAVID TIBBS, M.C.

FIRST ASSISTANT, DEPARTMENT OF SURGERY, ROYAL VICTORIA INFIRMARY, NEWCASTLE-UPON-TYNE, AND THE UNIVERSITY OF DURHAM; FORMERLY SURGICAL REGISTRAR, GUY'S HOSPITAL

OVER the last fifty years a few cases have been described in which the patient has developed an angiomatous tumour preceding the appearance of numerous further angiomata in the skin and other tissues; these tumours have rapidly increased in size and number, eventually causing the death of the patient. Microscopical examination has often shown that these angiomata lack obviously malignant histological qualities; accordingly some writers have used the paradoxical title of 'benign metastasizing angioma' for this condition.

The case about to be described appears to be typical of this series and it is put on record in the hope that it may contribute to the necessarily slow accumulation of knowledge about this rare disease.

CASE REPORT

HISTORY.—Mrs. T., aged 37, first noticed a tumour in her right breast in June, 1948, during the eighth month of her third pregnancy. At this time the swelling was ill-defined and was attributed to milk engorgement. Childbirth was normal and breast feeding was successfully carried on for seven months, the child being weaned in the eighth month, February, 1949. The left breast diminished in size with the cessation of lactation, but the right breast, although showing some decrease in size, became much harder than the left. In the months that followed the right breast underwent progressive enlargement. The patient, however, did not consult her doctor until a second swelling appeared under the left breast one year after the birth of her child.

At this time she was seen by Mr. W. G. Gill, who performed an excision biopsy of the smaller second tumour. The section confirmed the clinical diagnosis of angioma, and the patient was transferred to Guy's Hospital.

ON EXAMINATION.—She was a relatively well-nourished woman, who stated that she had gained rather than lost weight and, apart from some lassitude, felt well in herself. For the last three months her periods had become scanty but more frequent, lasting for a day and occurring every three weeks.

In the upper and inner quadrant of the right breast there was a large rounded swelling some 4 in. in diameter (*Fig.* 525). The skin overlying this mass was greatly discoloured, varying from bright red to a dusky cyanotic hue and markedly warm. In one area the skin was stretched over a soft fluctuant elevation which threatened to ulcerate. Numerous enlarged blood-vessels were evident coursing from a wide area into the tumour. The consistency varied from soft to moderately firm, and one area was fluctuant. The edge was ill-defined and the whole mass firmly attached to the underlying pectoralis muscle and inseparable from the rest of the breast. Where the colour changes were most marked, the skin

was firmly adherent, but elsewhere was movable over the tumour. There was no *peau d'orange* and no skin nodules were evident, although there were two small dark red papules on the outer side of the breast which could be blanched and reduced in size by pressure.

FIG. 525.—The right breast before mastectomy in October, 1949.

There was no associated lymph-gland enlargement. In short the tumour looked an angiomatous mass that had arisen in the breast and was in the process of bursting its way through the skin.

The site of the excision biopsy under the left breast showed a well-healed scar. Two small angiomata were noticed on the patient's upper abdomen, and a subcutaneous swelling was located just beneath the right scapula. This latter, which was about 1 in. across, soft, and could be emptied on pressure, was later confirmed as angiomatous. Mrs. T. had no knowledge of the existence of these lesions, which were almost certainly of recent origin. General examination failed to show any further abnormality.

AT OPERATION.—As the main tumour threatened to bleed copiously, it was decided to perform simple mastectomy. The operation proved uneventful in spite of

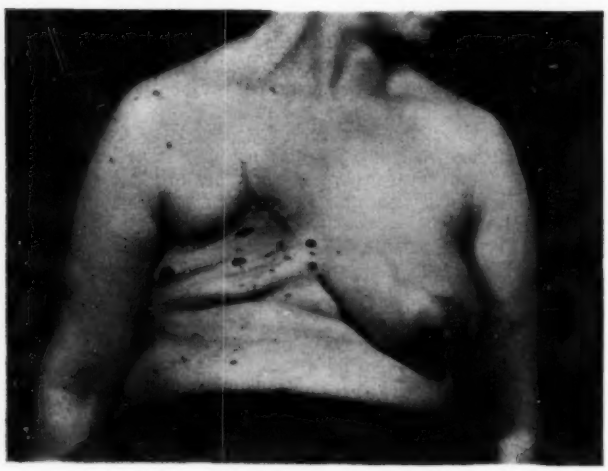

FIG. 527.—The same region as *Fig.* 526 in February, 1950, showing increased number and size of angiomata.

many alarmingly large vessels supplying the tumour and several angiomatous extensions into the pectoralis muscle. Wound healing was prompt and the patient returned to Guildford for radiotherapy to the remaining lesions (*Fig.* 526).

PROGRESS.—In the months that followed, the patien showed a rapid increase in the extent of her condition In December, 1949, she complained of lower backache which increased in severity to such a degree that, although X-ray plates at this time showed no abnormality, th

FIG. 526.—The chest following mastectomy. Several angiomata are visible in the skin surrounding the scar.

deep X-ray therapy which was being given to her skin lesions was transferred to her lumbar spine. This brought some relief, but by January, 1950, it was evident that the subcutaneous angioma under the right scapula was increasing in size in spite of radiotherapy. In February all doubts as to the malignant nature of the

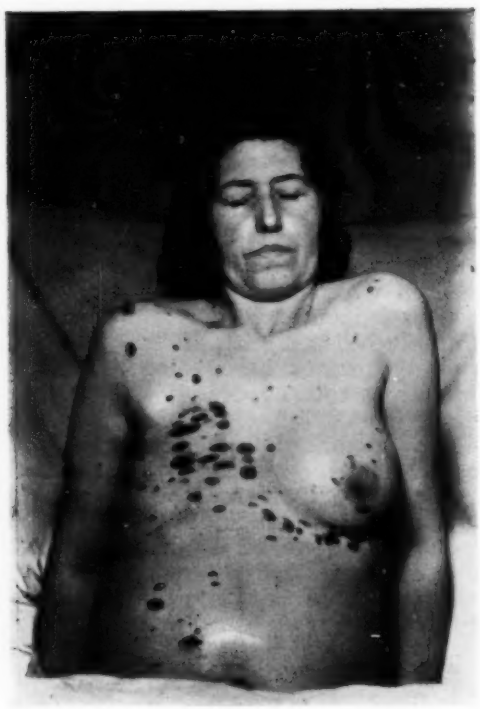

FIG. 528.—Appearance presented in June, 1950, showing the great increase in angiomata and marked emaciation of the patient. The back showed very similar changes.

process were dispelled by the unequivocal enlargement of the skin lesions on the abdomen and the appearance of a number of fresh angiomata scattered over the trunk (*Fig.* 527). There had developed, too, clear evidence of further internal deposits, as rectal examination revealed

a painless mass about 3 in. across in the pouch of Douglas. By March her backache was once more becoming severe and spinal movements were limited by pain and spasm of the erector spinæ muscles. The pelvic tumour by now had enlarged sufficiently for it to be easily palpable above the pubes. Weight loss was marked.

During April and May the patient did not attend hospital and it was learnt that she was in bed at home. Re-admission to Guy's was arranged in June, 1950. Her condition by now was most distressing. Her pale skin was covered with bright red tumours and her abdomen was grossly distended, partly by a massive tumour and partly by fluid (*Fig.* 528). By contrast her chest and limbs were wasted and the lax skin attested to the rapidity of weight loss. She lay flat in the bed as any attempt to change her position caused her the most intense pain in the back. In spite of the obvious gravity of her condition she was remarkably cheerful. A more detailed examination showed that she was profoundly anæmic (hæmoglobin —20 per cent) with a resting pulse of 130. The huge pelvi-abdominal mass was for the most part firm, but with several localized fluctuant areas, its surface being somewhat irregular. Mobility was slight and no bruit audible. All the skin and subcutaneous lesions showed the physical characteristics of blanching and diminution in size on pressure, with a fairly prompt return of colour and bulk on release. X-ray examination of the back showed partial collapse of the second lumbar vertebra. Ophthalmoscopy failed to reveal any retinal lesion.

Over the next month the patient gradually declined in strength and the angiomata grew relentlessly. A week before she died, pain and swelling of the left arm developed; this was clearly caused by the growth of yet another tumour behind the clavicle, for both supra- and infra-clavicular fossæ were markedly distended by an ill-defined swelling. Pitting œdema of the legs, which at first had been slight, was now pronounced.

In mid-July the patient abruptly developed a left-sided hemiplegia and lapsed into a coma. The next day she died without recovering consciousness.

At Autopsy.—(Dr. E. J. Navasquez.)

General.—The skin was covered with some one hundred and forty raised and rounded, sharply circumscribed purplish nodules varying in size from 1 mm. to 12 mm.

Cardiovascular System.—The pericardial sac contained a slight excess of clear fluid. Some twelve purplish nodules were present on the pericardial surface of the heart, which was otherwise normal.

Respiratory.—The two left lobes of the lung each contained two pale nodules some 2 cm. in diameter. The lymph-glands showed no change.

Abdomen.—The abdominal cavity contained approximately three pints of yellow fluid and was occupied almost entirely by a large mass arising from the pelvis. The liver was asymmetrically enlarged to about twice the normal size. The right lobe contained a rounded, sharply defined, hæmorrhagic mass 14 cm. in circumference, the cut surface of which was mottled by friable red areas and pale firm ones. Several smaller, but similar, areas were present in the left lobe, the smallest of which resembled the common type of cavernous hæmangioma.

The spleen was twice the normal size and showed one large and one small tumour similar to those in the liver.

The para-aortic and peripancreatic lymph-glands were enlarged and reddish.

The kidneys were normal except for one small hæmorrhagic nodule in each and two small nodules in the left hilar fat.

The large pelvic mass was composed of enormously enlarged ovaries, which together weighed 5100 g. They were in close apposition, but readily separated without damaging their surfaces. The right ovary was 29 by 20 cm. and the left 17 by 13 cm., the surface being smooth and glistening, but the contour nodular and resembling polycystic disease. On section the right ovary showed many contiguous rounded areas mostly hæmorrhagic, some showing pale centres and occupying approximately 4 cm. of the periphery. The centre of the ovary was necrotic and composed of friable greyish-yellow material. The left ovary was similar, but without the central necrosis.

Central Nervous System.—The brain was asymmetrical and showed flattening of the convolutions of the right cerebral hemisphere, due to a rounded hæmorrhagic area 4 cm. in diameter in the anterior part of the right corpus striatum, which was the cause of her terminal left hemiplegia. Another small nodule was found in the temporosphenoidal lobe. The dura contained a solitary pedunculated hæmorrhagic nodule.

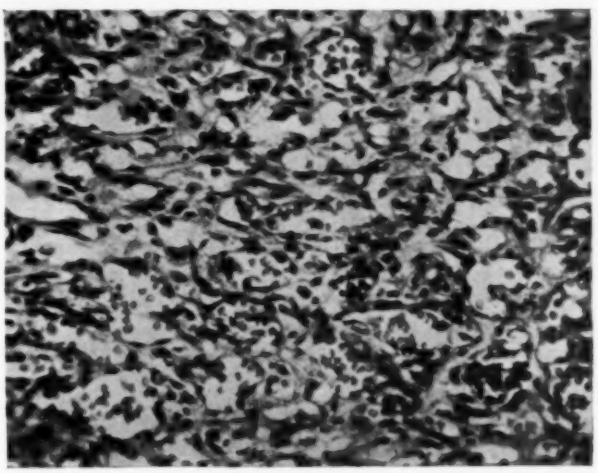

Fig. 529.—Photomicrograph of the primary breast tumour tissue, showing good differentiation, but definite endothelial proliferation in some places.

Skeletal.—The second and fourth lumbar vertebræ showed almost complete replacement of the body by hæmorrhagic tissue which had caused their collapse.

Microscopical Structure.—The primary breast tumour consisted of blood-containing spaces surrounded by flat, short, endothelial cells forming walls which were for the most part only a single layer. There were, however, areas of more cellular structure indicative of proliferation (*Fig.* 529).

Of the lesions found at post-mortem a skin section showed a hæmangioma composed of blood-containing spaces enclosed within single layered endothelium (*Fig.* 530). The kidney showed one minute nodule of great cellularity with very marked variation in size, shape, and staining properties of the cells, some of which were multinucleate (*Fig.* 531). The ovaries displayed great variation in structure, from endothelial cells forming a loose network mingled with red blood-corpuscles, to proliferating columns of cells (*Figs.* 532, 533). Many hæmorrhages were present and some areas showed far more completely differentiated tissue identical with that described in the primary breast tumour.

The lung showed in one place a fragment of angiomatous tumour in the lumen of a large vessel, probably a pulmonary vein (*Figs.* 534, 535).

All other slides showed similar appearances and those above are given as typical examples. The microscopical findings were characteristic of a malignant hæmangio-endothelioma.

DISCUSSION

The common hæmangioma is a tissue malformation of developmental origin and as such is an example of a hamartoma (Albrecht, 1904). It is not

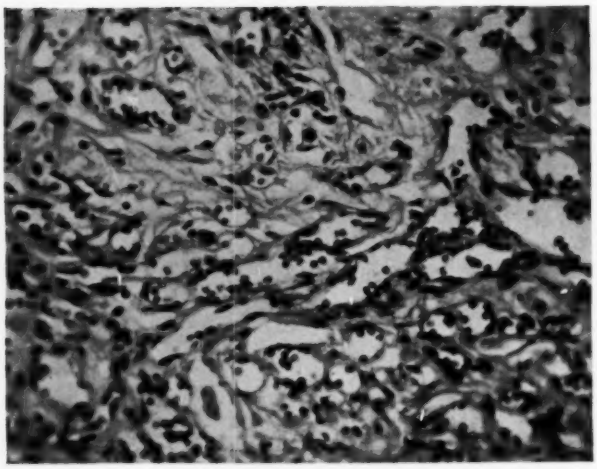

FIG. 530.—To show the benign appearance typical of many of the subcutaneous deposits.

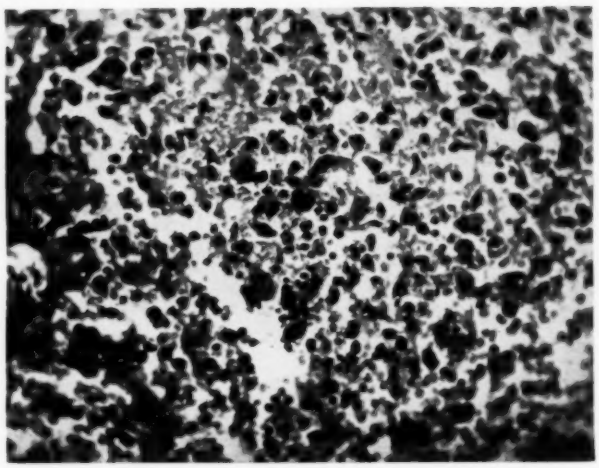

FIG. 531.—Section of a deposit in one kidney showing very marked pleomorphism and anaplasia.

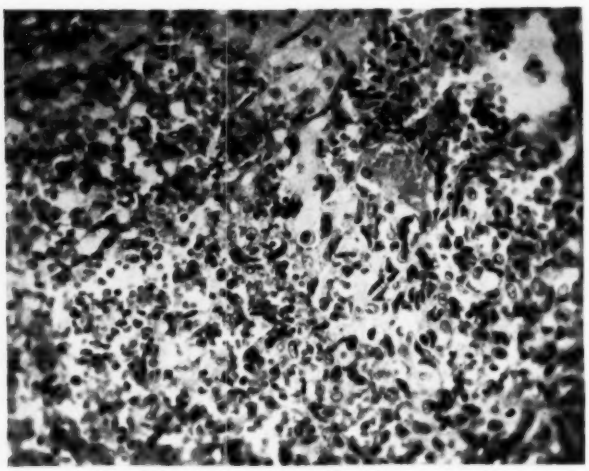

FIG. 532.—Section from one ovary showing an area of endothelial cells forming a loose network mingled with red blood-cells

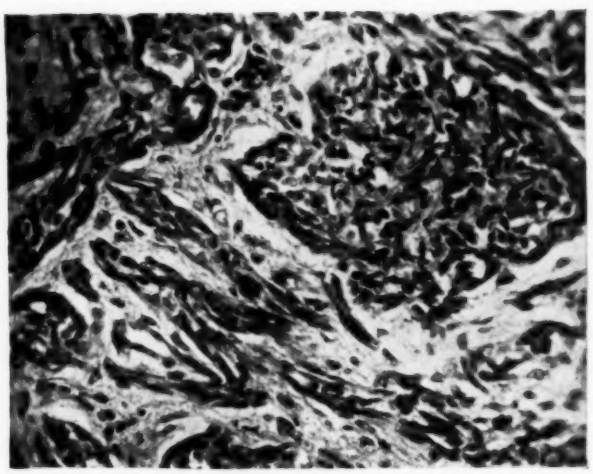

FIG. 533.—Another area in the same ovary showing endothelial cells proliferating in long columns.

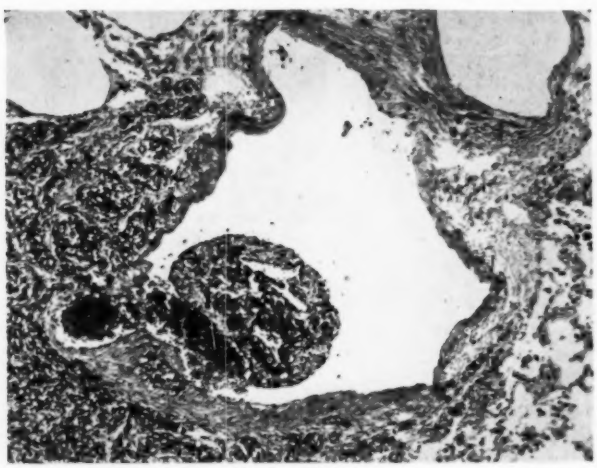

FIG. 534.—A well-differentiated fragment of angioma tissue lying free in one of the pulmonary vessels.

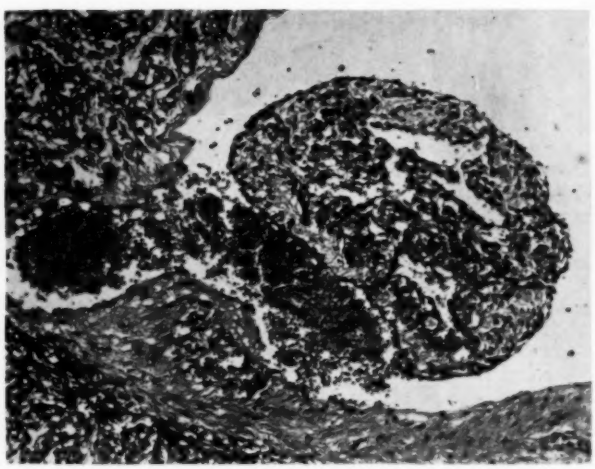

FIG. 535.—Greater magnification of *Fig.* 534 to show structure in detail.

strictly speaking a neoplasm at all and certainly is to be regarded as a benign condition. There are a few cases on record where such a hæmangioma has caused the death of the patient by impeding some vital function such as respiration or by bleeding uncontrollably into the peritoneal cavity. These events, however, are incidental and do not influence the conception of an essentially benign lesion.

Occasionally a hæmangioma will be encountered which grows rapidly and is soon followed by an ever-increasing number of actively growing hæmangiomata, so that the patient eventually dies with multiple growths all over the body, with practically no tissue or organ being spared. This is the dramatic course followed by the malignant hæmangioma, which is now recognized as being a metastasizing neoplasm. In the earlier part of this century several cases were described in which the authors were struck by the innocent histological appearance which belied the universally malignant course of the disease. Thus in 1906 Borrmann described a case very similar to the present one. Others have been described by Shennan (1914), Ewing (1928), and Geschickter and Keasbey (1935). The term benign metastasizing hæmangioma was given to this condition. In 1936 Robinson and Castleman described a case very similar to these above in which the first lesion to appear was disarmingly innocent, but the angiomata which subsequently developed had a characteristically malignant histology and indeed macroscopically invasive qualities. This case they felt bridged the gap between the ' benign ' and ' malignant ' metastasizing hæmangioma.

In 1943 A. P. Stout reviewed the position of this group of tumours and gave a clear description of his histological criteria of malignancy. He went on to consider the cases mentioned above and others that he had collected himself, and in every case concluded that from the outset it had been malignant and that at no stage were the lesions benign. By now the evidence was such that the old idea of a benign metastasizing lesion had become untenable.

A. P. Stout's comprehensive account brought together the recorded examples of this condition and made it clear that they formed a clinical and pathological entity. This entity must not be confused with the ' Kaposi ' sarcoma, which Willis (1948) considers may be a hæmorrhagic reticulosarcoma, nor with multiple benign angiomata developing in the skin or in selected organs which must be regarded as multi-focal hamartomata. The condition under discussion is a malignant hæmangioma (or more correctly hæmangio-endothelioma) which starts as a solitary lesion and progresses rapidly to involve indiscriminately every part of the body, the histology varying from well-ordered tissue to that in which the malignant character is undoubted. It is this considerable variation which delayed recognition of the true nature of the condition.

Now there remains a group of cases in which the patient dies with multiple hæmangiomata in certain organs only. Most examples have involved spleen and liver or the lung, but tissue outside these organs has not been involved. The microscopical appearances are decidedly malignant. These cases were described by Langhans (1879), Theile (1904), Jores (1908), Wright (1928), Paine (1931), and De Navasquez (1936). The latter regarded his case as having arisen in the spleen and metastasized to the liver. This restricted metastasis may well explain all the cases of this group. If this explanation is correct, then they form further examples of malignant hæmangio-endotheliomata. Their proper place, however, is not yet decided, as some authorities regard them as probable ' multifocal system lesions ' in preference to accepting a metastatic origin (Willis, 1948).

The case described in this paper was beyond reasonable doubt a malignant and metastasizing neoplasm of angioblastic tissue. It is therefore in the same category as those cases described by A. P. Stout (1943). The histology varied from that indistinguishable from the simple cavernous hæmangioma to the picture of malignant cells multiplying without any attempt at differentiation and showing clearly invasive qualities. Indeed any doubts were dispelled by the finding of a small embolus of well-formed angioma tissue lying free in one of the pulmonary vessels (*Fig.* 534). The ovaries at death contained massive angiomata. It could be suggested that the process started here and any breast and skin angiomata were metastases from these. Against this, however, is the appearance of the breast tumour a clear year before any other lesion was evident. Certainly at the time of mastectomy no ovarian tumour was detectable, but appeared only when numerous other deposits were evident. In short, the breast may reasonably be presumed to be the primary site. It is not impossible that in some cases multiple primaries appear which in their turn metastasize, but unless evidence of this is produced it appears wiser to assume that the whole process starts in one primary tumour and like any other sarcoma metastasizes from there. Certainly treatment should be based on this assumption and the initial angioma extirpated on diagnosis.

It is interesting to note that about one-third of the recorded cases of malignant hæmangioma started in the breast. The present case commenced during pregnancy; most other cases occurred in patients who were not pregnant. There appears to be no characteristic age, as cases are recorded ranging from infancy to the sixth decade, but young adults form the largest group. There is a distinct predilection for the female sex.

Diagnosis and Prognosis.—The angioma that appears where none has previously existed and grows rapidly should always be suspect. This is to be sharply distinguished from the angioma in a child present from birth, which undergoes some apparent extension or increase in bulk owing to further canalization or thrombosis. A biopsy will clarify the diagnosis in most cases, but in some the microscopist may be confronted by well-formed tissue with little to suggest malignancy. Biopsy then may be actually misleading in addition to being a very hæmorrhagic undertaking, carrying an unknown risk of spreading the tumour into the blood-stream. It is better that the solitary angioma of recent origin and rapid growth should be removed completely as an initial step if this be possible.

Local recurrence after removal is a most sinister diagnostic and prognostic sign. Presumably the

excision has not sufficiently widely cleared the margin of the growth. Borrmann's case (1906) recurred five times before metastasis became evident. Stout describes an orbital angioma of undoubted histological malignancy which recurred repeatedly.

Once metastases appear there is no known method of controlling further spread and the prognosis is hopeless.

Treatment.—Surgical removal was undertaken in the present case only after several 'secondary' tumours had appeared. Clearly the condition was already out of hand, but certain pertinent observations can be made to answer some fundamental questions.

If we wish to form some idea of when metastasis occurred in this case we may assume that the secondary growths grew steadily at roughly parallel rates. The slowest grew from minute skin angioma to tumours 1 cm. across, and the fastest from an intrapelvic tumour about 5 cm. across to one about 20 cm. across, all within the space of three months at a certain stage in the clinical history. Allowing for the probable logarithmic growth expansion one can guess from these rates that the time taken for a malignant embolus to grow from microscopical dimensions to a clinically detectable lesion would be under six months. Now the first metastasis became evident one year after the primary tumour first appeared, so it is not an unreasonable assumption to say that the primary tumour was growing for at least several months before metastasis took place. At this stage surgical excision is imperative and offers the only slender chance of cure.

Our next consideration is the extent of surgical excision necessary. In the present case the breast tumour, although vast, was not associated with any lymph-gland enlargement and at no time did the lymph-glands play a prominent part. It is true that at the post-mortem examination some of the para-aortic glands were affected, but these may well have been blood-borne deposits. It seems unnecessary, therefore, to make any attempt to remove the regional lymphatic glands. Wide surgical excision of the primary tumour appears adequate.

Radiotherapy had a temporary retarding effect on a subcutaneous deposit and caused some easing of the pain due to spinal metastases. The effect, although minimal and transitory, suggests that radiotherapy should be employed as an adjunct to surgery.

It would appear theoretically possible to remove the primary tumour at an early stage with the possibility of complete cure. In short, there is justification for treating the malignant hæmangioma just as one would its related lesion the fibrosarcoma. An intense course of radiotherapy followed by wide surgical excision without lymph-gland clearance should be the basis of treatment. Amputation of a limb would apparently offer little advantage if wide excision was possible without. If the condition is widespread, there is no known effective treatment. Palliative radiotherapy brought a short remission of pain in our case and has had a decided effect, although temporary, in others (Robinson and Castleman, 1936).

SUMMARY

A case of malignant hæmangio-endothelioma is described.

The property of unequivocal growth is the one distinctive feature in the early case. The histological picture from an isolated biopsy may still leave the diagnosis in doubt.

Present knowledge of this very rare condition indicates that a rapidly growing hæmangioma of recent origin in child or adult should be regarded as a probable malignant hæmangioma and wide surgical excision should be undertaken, preferably supported by pre-operative radiotherapy.

Such a course of action will only very occasionally be demanded. The common innocent cavernous hæmangioma of developmental origin may increase in size owing to thrombosis, infection, further canalization, and growth proportional to the body. This must be sharply distinguished from the progressive growth of the malignant condition.

I wish to express my gratitude to Mr. Hedley Atkins for permission to publish this case and for his invaluable advice. I am indebted to Dr. S. J. De Navasquez for his encouragement to draw freely from his post-mortem and histological reports, coupled with advice on numerous aspects of this case.

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CHRONIC JEJUNAL PROLAPSE FOLLOWING GASTRO-ENTEROSTOMY

By J. E. RICHARDSON

ASSISTANT DIRECTOR, SURGICAL UNIT, AND ASSISTANT SURGEON, THE LONDON HOSPITAL

JEJUNAL prolapse through a gastro-enterostomy is a rare condition and the following two cases are therefore worth recording.

Sten Aleman (1948) reviews the literature of the 70 reported cases, which includes both the acute and chronic types, and gives a bibliography of sixty-seven references.

CASE REPORTS

Case 1.—Mrs. F. P. (L. H. record No. 44112/50), aged 70, was sent to the London Hospital on Oct. 20, 1950, with a letter from Dr. Cronin stating that she had had severe nausea and loss of appetite for several weeks. A barium meal was done by Dr. Wilson-Sharpe and showed the typical appearance of jejunal prolapse through a gastro-enterostomy (*Fig.* 536).

FIG. 536.—*Case* 1. Two radiographs showing the jejunal prolapse and general tone and outline of the stomach.

Background: Born Jan. 22, 1880, the eldest of ten children, she had a hard childhood looking after the younger children. In 1894 she went into domestic service, but as her health was bad she soon gave this up and made envelopes. In 1900 she married and there were 6 children. In 1925, at the age of 45, she began to get epigastric pain, vaguely related to food, and in 1928 a gastro-enterostomy with pyloric occlusion was done in the London Hospital. According to the operation notes there was a huge ulcer on the posterior surface of the pylorus and a second smaller ulcer on the lesser curve of the stomach. From 1928 to 1940 she remained fairly well and lived at home with her husband in a flat. From 1940 to 1947 she complained of increasing palpitation and shortness of breath on exertion. In September, 1948, she was an in-patient in the London Hospital under the Cardiac Department and an electrocardiogram then suggested a possible infarction. At that time her blood-pressure was 210/110, Hb 67 per cent, colour index 0·96.

In November, 1950, following the radiologist's report, she was admitted as an in-patient under the Surgical Unit for gastroscopy, but unfortunately this proved impossible owing to a thoracic kyphosis. Since then she has attended Medical Out-patients at regular intervals. Her last visit was in February, 1952. Her weight has remained fairly constant at about 8 st. 8 lb. and her Hb remains at about 75 per cent. She continues to complain of some tiredness and headaches and her stomach remains "much about the same".

Case 2.—Mrs. J. O. (L. H. record No. 19094/51), aged 33, first attended the London Hospital on May 22, 1951, with a letter from Dr. Payan saying that she had been vomiting ever since her gastro-enterostomy in January, 1951, and that her gastro-enterostomy opening had almost completely closed. A barium meal by Dr.

Howarth showed the typical appearance of jejunal prolapse through a gastro-enterostomy (*Fig.* 537).

Background : Born Feb. 21, 1918, an attractive-looking Irish woman, she gave the impression of being vague and happy-go-lucky. After leaving school she worked at ladies' tailors until she married in 1945. She has had

FIG. 537.—*Case* 2. Radiograph showing stomach with the jejunal prolapse.

two children. She is a non-smoker and a teetotaller. Symptoms began in 1939, at the age of 20. There was no real pain, but acid eructations at times were so severe that they led to true vomiting. A posterior gastro-enterostomy was done in Cork, Ireland, on Jan. 6, 1951, but this failed to relieve her symptoms.

Following the barium meal report she was admitted to the London Hospital under the Surgical Unit in June, 1951. The prolapsed jejunal mucosa was well seen at gastroscopy on June 4, 1951, and the appearance was sketched by Miss Archer, the hospital artist (*Fig.* 538). On June 6 a partial gastrectomy was done with a Bilroth I type of anastomosis. No intussusception was found at the time of operation ; the duodenum appeared normal but the pylorus was constricted. On July 3 she was seen in the follow-up clinic, her weight had increased from 7 st. to 7 st. 7 lb., there was some epigastric discomfort with palpitations after a full meal, but she was very pleased with herself.

She has now returned to Ireland. In her last let dated Sept. 15, 1952, she says she is still well satisfied w a surgical stomach though she has a little regurgitation

Discussion.—In *Case* 1 surgical treatment w not recommended. The patient was over 70, h general health was poor, and there were no seve symptoms. At a subsequent X-ray examination was seen that the prolapse reduced itself spo taneously when the stomach dilated.

In *Case* 2 partial gastrectomy seemed to be t correct treatment. The patient was young, h

FIG. 538.—*Case* 2. Gastroscopic view of the distal end of the stomach, with the jejunum appearing through the stoma of the gastro-enterostomy.

general health was good, and she lived in a countr district in Ireland. The gastro-enterostomy ha failed and at times her symptoms were severe. A operation the prolapse was not seen ; possibly it wa reduced while her muscles were relaxed under th anæsthetic, or when the stomach was lifted to se the posterior surface. The type of gastro-enteros tomy was slightly different from that which used to be done in the London Hospital. The afferen loop was relatively long and the stoma wa placed horizontally near the greater curvature o the stomach.

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GIANT NEUROFIBROMA OF THE GREAT OMENTUM

By H. ORISHEJOLOMI THOMAS and D. B. JELLIFFE
FROM THE DEPARTMENTS OF SURGERY AND MEDICINE, UNIVERSITY COLLEGE, IBADAN, NIGERIA

Cases of visceral neurofibromatosis are rare; King (1917) found report of only 3 cases of neurofibromatosis of the intestine in 119 non-malignant intestinal tumours. Raiford (1932), from 11,500 autopsies and 45,000 surgical specimens at Johns Hopkins Hospital, was able to collect 88 cases of primary benign and malignant tumours of the small intestine, out of which there was not a single example of neurofibroma. Visceral neurofibroma usually affects the ileum, although the mesentery or colon may sometimes be involved. Malignant change occurs in about 13 per cent of cases (Hosoi, 1931).

Grill and Kuzma (1942) reported a case of a woman of 60 who had generalized neurofibromatosis. She was suffering from recurrent severe gastro-intestinal bleeding. A lower abdominal mass which was mobile and painless was found on examination. She died before an operation could be performed. At autopsy a circumscribed tumour of the ileum was found 18 cm. proximal to the ileocæcal junction. It arose within the muscle layer of the antimesenteric surface, and measured 6·5 by 5·5 by 4 cm. Its surface, which was smooth, had engorged veins coursing over it. In consistency it was moderately soft, but remained firm on sustained pressure. The cut surface was homogeneous and its colour pinkish-grey. Summary of the findings on microscopical examination was as follows :—

1. *Ileal tumour*: Sections stained with hæmatoxylin-eosin showed that the stroma of the tumour was composed of distinct bundles of reddish-staining tissue forming definite whorls and tracts. The bundles were formed by a parallel arrangement of wavy collagenous fibres with elongated granular nuclei. Careful search showed that some cells were present which had scanty cytoplasm, and relatively large vesicular nuclei. These were thought to be Schwann cells. An outstanding feature of the sections was the presence of numerous thin-walled blood-spaces. With Masson's trichrome stain the collagenous matrix was stained green, with a tinge of purple here and there. Bundle tracts formed of fine reticular fibres lying along the long axis of the nuclei were demonstrated by the silver impregnation method.

2. *Skin nodule*: Sections stained with hæmatoxylin-eosin showed " dense uniform reddish-staining collagen matrix containing elongated, oval or pointed nuclei, with compact granular bluish-staining chromatin substance ". With Masson's trichrome stain, " the matrix appeared as a greenish-staining substance with nuclei scattered throughout the sections ". Sections of the skin nodule differed from those of the ileal tumour in that the tissues showed no formation of whorls or bundle tracts, and no nervous element was present. They concluded that the skin nodule was a fibroma, and that basically the cytological picture of the ileal tumour fitted in with those of tumours of von Recklinghausen's disease described by various authors.

In some cases no cutaneous nodules are found. Such a case was reported in a 30-year-old man by Poate and Inglis (1928). Their findings were ganglioneuromatosis of the ileum and ascending colon. The tumour masses were composed mainly of fibrocellular tissue bearing no resemblance to nerves, although in parts abnormal nerve-trunks and ganglion cells were present.

Mesenteric neurofibromatosis was reported by Barton and Inglis (1931). The patient was a man of 40 who had recurrent attacks of bleeding per rectum. Cutaneous lesions of molluscum fibrosum were present. At operation a mass formed of numerous white nodules was found involving about 8 in. (20 cm.) of the mesentery, at a distance of about 4 ft. (120 cm.) from the ileocæcal junction. Resection of the mass and related ileum was performed, and continuity of the bowel restored by end-to-end anastomosis. The pathologist reported: " Mesentery contains a collection of irregularly rounded tumours composed chiefly of old fibrous tissue. In the larger nodules no resemblance to nerves is apparent, but in the smaller nodules the structure is less dense, the tumour more cellular, and they show a distinct resemblance to nerves." Their conclusion was that the lesion in the mesentery was of the same type as those in the skin.

We have so far been unable to find any reference to neurofibroma arising in the great omentum, and we consider the case reported below to be of special interest.

CASE REPORT

Y. A. a young male Nigerian, of about 20 years of age, belonging to the Yoruba tribe, was admitted on December 27, 1950, under the care of one of us (D. B. J.), with an abdominal swelling. He complained of general weakness, and of his abdomen getting gradually bigger for the past four months. There was no abdominal pain, no vomiting, and no change in bowel habits—the bowels being moved once or twice daily.

On Examination.—He was a thin man, not anæmic, and had clubbing of his fingers. There were multiple, small, soft, sessile, rounded tumours projecting from the skin, each measuring about 0·12 in. (0·3 cm.) in diameter. Similar but larger intracutaneous tumours, measuring about 0·25 in. (0·6 cm.) in diameter, could also be felt, but these had not produced visible nodules. They were painless and had been present for about six months. The sessile tumours of the skin were scattered about the chest and arms, and the intracutaneous nodules, which were more numerous, were found mostly on the abdomen and the back. Hyperpigmented areas, ovoid in shape, and varying in measurement from 1·4 in. by 0·6 in. (3·5 cm. by 1·5 cm.), to 0·8 in. by 0·4 in. (2 cm. by 1 cm.) were distributed as follows: three on the left side of the chest, several on the lower half of the back, and two on the back of the neck. There was no scoliosis or other abnormalities of bone. An enormous abdominal tumour was palpable. It occupied the greater part of the abdomen. It was slightly bi-lobular, firm in consistency, and its surface felt nodular. There was no tenderness. It was fairly mobile from side to side, though movement

up and down was more limited (*Fig.* 539). An attempt was made to correlate the abdominal mass with the cutaneous findings, which were diagnosed as neurofibromatosis. The abdominal mass was therefore thought to be a visceral neurofibroma undergoing sarcomatous change, in view of its rapid enlargement in so short a time. Since there was no intestinal upset, in spite of its enormous size, and in view of its mobility laterally, it was decided that the tumour was arising from the great omentum or mesentery. A barium meal examination and follow-through showed no obstruction of the gut. The blood-count was normal.

FIG. 539.—Before operation. The tumour outlined.

FIG. 540.—After operation.

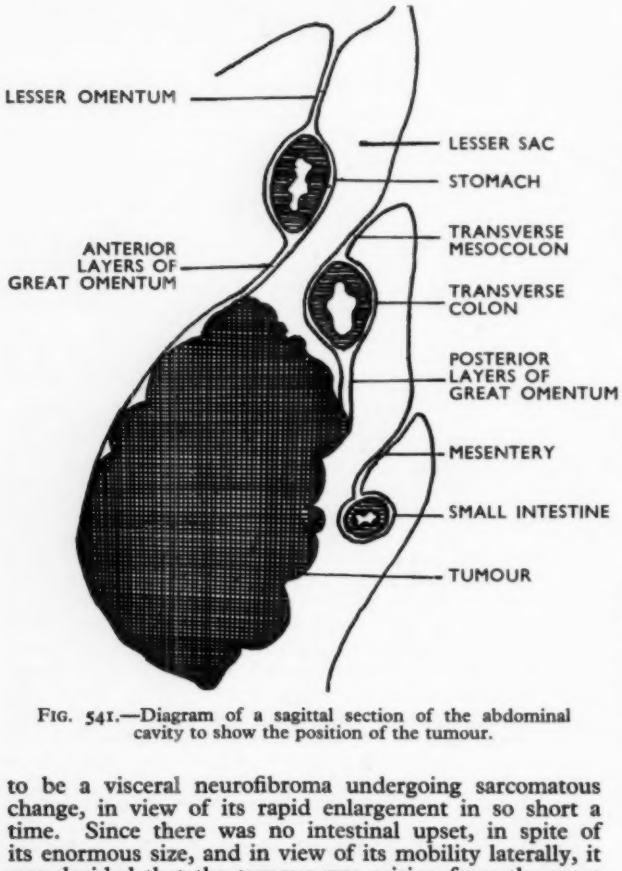

FIG. 541.—Diagram of a sagittal section of the abdominal cavity to show the position of the tumour.

AT OPERATION (H. O. T.).—Laparotomy was performed on January 11, 1951, under spinal anæsthesia (12 c.c. 1-1000 decicain given by Dr. R. J. Stout). A median incision extending from the tip of the xiphoid process to half-way between the umbilicus and the symphysis pubis was made. A large tumour which seemed to be contained between the layers of the great omentum was found occupying most of the abdomen (*Fig.* 541). It was attached by a small 'stalk' about 2 in. (5 cm.) long, and about 0·1 in. (0·25 cm.) in diameter, to the posterior surface of the stomach. The 'stalk' was divided at its attachment to the stomach, and as there was no infiltration of the stomach wall, it was concluded that it was merely a fibrous adhesion between the two structures. The tumour was delivered on to the anterior abdominal wall without difficulty, and its upper border was found to be continuous with the great omentum.

It was excised by 'clipping and cutting' the great omentum just above the tumour, and by dividing a few adherent bands attaching the tumour to the flanks. The stomach and small and large intestines were normal, as were the spleen, liver, and mesenteric glands. The abdominal wound was closed in layers.

The patient made an uneventful recovery, and was discharged from hospital eleven days after the operation. (*Fig.* 540.)

THE SPECIMEN.—A solid tumour, somewhat hemispherical in shape. The remains of the anterior layers of the great omentum, containing dilated veins, covered the anterior surface of the tumour and were adherent to it. The posterior surface was more nodular than the anterior. Round its widest part its circumference was 42 in. (105 cm.), and it weighed 17½ lb. (7900 g.). There were three other nodules about ½ to 1 in. (1·75 to 2·5 cm.) in diameter which were attached to the posterior surface of the main tumour by pedicles. The cut surface was firm and fleshy, but showed areas of cystic degeneration towards the centre. (*Figs.* 542-544.)

PATHOLOGICAL REPORT (*Dr. W. D. Silvera*).—

1. *On biopsy of two nodules from skin and subcutaneous tissue*: "Specimen consists of two hard nodules, measuring about 1 cm. in diameter, covered by skin.

Cut surface shows very firm white dense fibrous tissue and skin. Sections of nodules show intact skin with fibromatous nodules underneath. Nerves are seen in the sections, but no specific stains have been done." (*Fig.* 545.)

2. *On sections of the tumour* : " Sections show growth composed of masses of fibrous tissue cells, arranged in bundles running in different directions. Cells vary in size. In parts they are laying down fibrils. In others they are more primitive, the nuclei varying in size. There are many thin-walled vessels but no hæmorrhages. Mitoses are scant. The features are those of a very cellular fibroma. Early malignancy. Fibroma." (*Figs.* 546, 547.)

Unfortunately at the time of examination it was not possible to carry out special nervous tissue staining.

DISCUSSION

Clinically the case was one of abdominal tumour in a man showing cutaneous neurofibromatosis. A diagnosis of visceral neurofibroma was made.

FIG. 542.—Anterior view of the tumour. The vessels of the anterior layers of the great omentum can be seen coursing over it.

Presumably the tumour arose from autonomic nerve-fibres derived from the cœliac plexus, and accompanying the omental branches of the gastro-epiploic arteries. Although the histological appearances of the tumour and of the skin nodules are reported as being those of a fibroma, we are inclined to retain our clinical diagnosis of neurofibromatosis. As is well known, the histological diagnosis of neurofibromata presents a problem in as much as the elements forming nerve-sheaths have a dual origin, i.e., ectodermal (neurolemmal or Schwann sheath), and mesodermal (perineurium and endoneurium). In a tumour derived from a nerve-sheath, the ectodermal or the mesodermal element may predominate, sometimes almost to the complete exclusion of the other. Stewart and Copeland (1931) have shown that neurofibromata may be wholly or predominantly fibroblastic in nature and that a thorough examination in the majority of fibromata or fibrosarcomata of doubtful origin would produce evidence of their arising in relation to nerves. Another reason why

FIG. 543.—Posterior view of the tumour. The nodularity of the posterior surface is well shown.

FIG. 544.—Cut surface of the tumour, showing cystic degeneration towards the centre.

a neurofibroma may present a histological appearance indistinguishable from that of a fibroma is that Schwann cells are capable of forming collagen (Murray, Stout, and Bradley, 1940). The structure of neurilemmomas lends support to this view, for the

histology may vary from well-regimented growths with fibres staining unlike collagen, to those possessing dense collagenous fibres resembling ordinary fibromata (Willis, 1948). The same author further

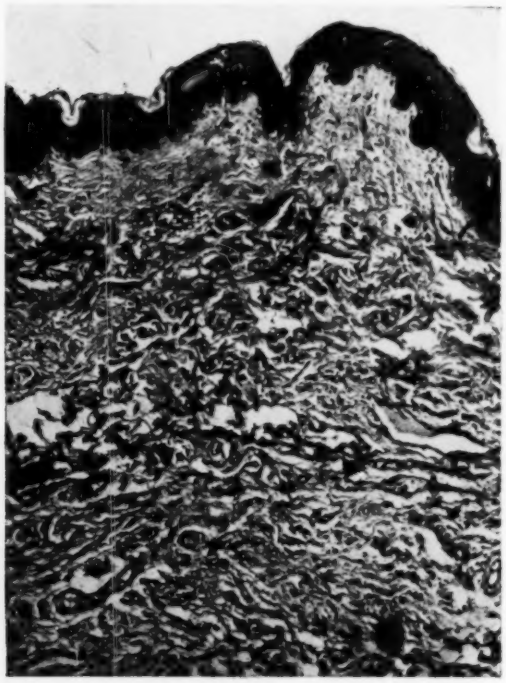

FIG. 545.—Section of a skin nodule showing its fibromatous appearance. (× 84.)

suggests that both components of the nerve-sheath, though derived from distinct sources, may form a unified system in which the cell properties vary

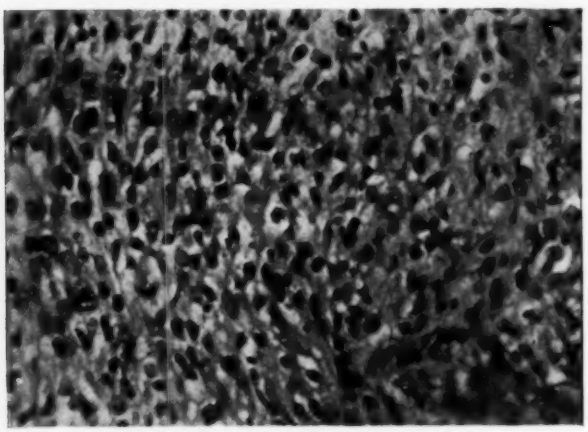

FIG. 547.—High-power view of a section of the tumour. (× 300.)

according to their proximity to the nerve-fibre. "Adoption of this view", he continues, "would largely resolve the difficulties in interpreting the structure of nerve-sheath tumours. According to it we might expect to encounter tumours of distinctive Schwann-cell type, others of non-distinctive mesenchymal type, and others of associated, combined, or transitional type. And this in fact is what we find."

There are, therefore, two possible explanations for the histological picture in our case. Either the Schwann cells of the neurilemmal sheath had produced excessive collagen, or the tumour was

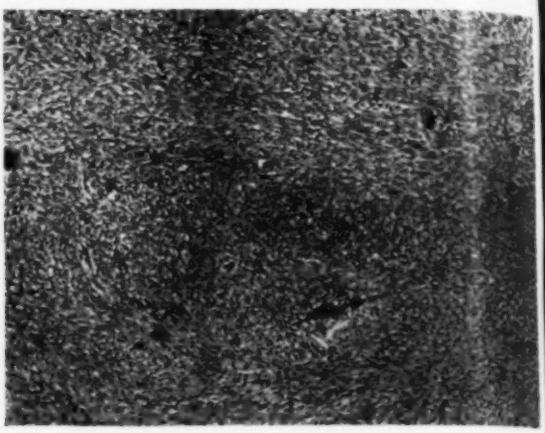

FIG. 546.—Section of the tumour showing arrangement of fibrous tissue cells and deposition of collagen. (× 72.)

derived almost exclusively from the mesodermal elements of the nerve-sheath. It is of interest to note that in none of the three cases referred to above (Grill and Kuzma, 1942; Poate and Inglis, 1928; and Barton and Inglis, 1931), was an unequivocal histological diagnosis of neurofibromatosis made in sections of skin or visceral lesions. Only by forming a composite picture of the clinical and pathological findings was such a diagnosis arrived at; and the same has been our experience.

SUMMARY

The scanty literature of visceral neurofibromatosis is briefly reviewed. A case of an enormous neurofibroma of the great omentum occuring in a young man suffering from cutaneous neurofibromatosis is reported, and its operative removal is described. Histologically the tumour resembled a fibroma. Possible explanations of this are considered.

Thanks are due to the following: Dr. W. D. Silvera for reporting on the histological appearance of the two specimens; Professor F. A. R. Stammers, Department of Surgery, University of Birmingham, for helpful criticism; Professor C. F. V. Smout, Sub-Dean and Tutor, Medical School, University of Birmingham, who kindly arranged for the photomicrographs; Mr. W. J. Pardoe, artist to the Birmingham Medical School, for taking them; and Mr. A. Paterson, for taking photographs of the tumour.

We are indebted to Professor Beatrice M. Joly, Department of Surgery, and to Professor A. Brown, Department of Medicine, University College, Ibadan, for permission to publish this paper.

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LEIOMYOSARCOMA OF THE BLADDER

BY M. V. P. PEIRIS AND G. H. COORAY, COLOMBO, CEYLON

PRIMARY sarcoma of the bladder is a tumour which is rarely seen. In a review of 151 cases, Crane and Tremblay (1943) found that the great bulk of tumours were either leiomyosarcomata or fibrosarcomata. According to them bladder sarcomata grow rapidly and infiltrate locally, the majority of the patients dying in less than six months. There appears to be a diversity of opinion regarding the occurrence of metastases. Albarran (1891) states that metastases occurred in 13·2 per cent of his cases, Munwes (1910) in 52 per cent, and Cecil (1926) in 21·7 per cent; but Concetti (1900) found metastases only once in 42 cases, and according to Mixter (1917) sarcomata of the bladder do not tend to metastasize. Ashburn and Wollenweber (1938) recorded a leiomyosarcoma without metastases and Jones and Ross (1950) reported a case of osteogenic leiomyosarcoma where the patient was found to be free from recurrence or metastases nine months after a conservative type of operation. In this paper is reported a case of leiomyosarcoma treated by total excision of the bladder after ureteric transplantation. The patient is alive and well and free from metastases two years after operation.

CASE REPORT

H. M., a married Sinhalese woman 32 years old, was admitted to the General Hospital, Colombo, on May 5, 1949, complaining of burning sensation on micturition for two months and passage of blood in the urine on and off during this same period.

Her family history was irrelevant and there was no illness of any significance in her past history.

She was rather pale and wasted. A hard tender mass which appeared to arise from the pelvis was palpable just above the symphysis pubis, extending about 2 in. upwards. It was about 4 in. in width. On vaginal examination, however, it was not possible to feel this mass separate from the uterus.

While in hospital she passed blood-stained urine from time to time, the urinary deposit always showing a large number of red cells and pus cells. Her blood-count was as follows: R.B.C. 3,900,000 per c.mm., W.B.C. 8000 per c.mm.; Hb 75 per cent (Sahli); Polymorphs 55 per cent, lymphocytes 40 per cent, and eosinophils 5 per cent. Erythrocyte sedimentation rate (Westergren method): 1 hour 24 mm., 2 hours 58 mm. A culture made from the urine grew *B. coli* and non-hæmolytic streptococci. A plain radiograph of the genito-urinary tract showed no abnormality. Cystoscopic examination revealed a large growth in the bladder and it was decided to perform a total cystectomy after transplantation of the ureters.

As her general condition and the anæmia did not warrant immediate operation, she was given adequate pre-operative treatment which consisted of the administration of hæmatinics, giving her a good diet and transfusing her with blood.

Two months after her admission to hospital, transplantation of both ureters to the colon was performed and six weeks later a complete cystectomy by a transperitoneal approach was carried out. The appendix was removed simultaneously. The bladder, at operation, was ovoid in shape and measured about 5 × 4 in., and appeared to be almost entirely occupied by a large tumour. No deposits were seen on the serous coat

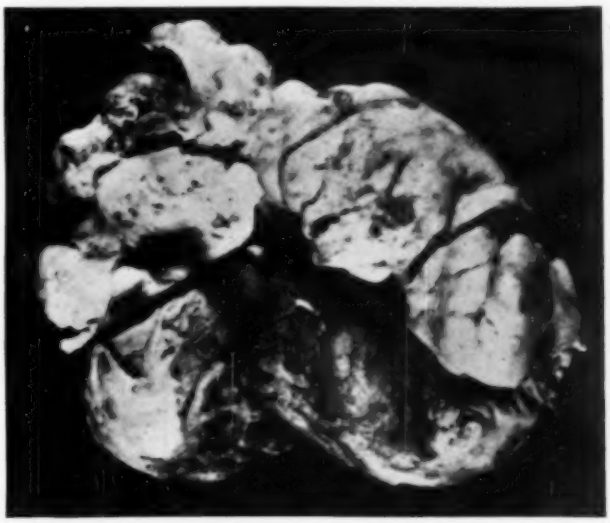

FIG. 548.—A gross photograph of a large fleshy polypoidal mass.

and as far as could be ascertained at operation, no secondary deposits were found in the peritoneal cavity.

POST-OPERATIVE COURSE.—300 c.c. of blood and 1 pint of 5 per cent glucose in normal saline were administered immediately after operation. Except for a slight discharge from the wound and frequency of micturition per rectum which lasted only for a few days, her recovery was uneventful. She left hospital on Sept. 21, 1949, about five months after her admission, and a radiograph of the genito-urinary tract after intravenous uroselectan showed that both kidneys functioned. There was a slight hydronephrosis in the left kidney. The lung fields were clear both at the time of admission to and discharge from hospital.

She was last seen in March, 1951, nearly two years after her admission to hospital and was quite well and free from urinary symptoms. As far as could be ascertained clinically and radiologically, she was free from metastatic deposits. Intravenous pyelography showed satisfactory function of both kidneys.

DESCRIPTION OF TUMOUR.—

Macroscopical.—The tumour, which was whitish in colour, invaded the bladder wall for varying depths and

projected into the lumen of the viscus in the form of fleshy polypoidal masses (*Fig.* 548), which were so large as to cause considerable diminution in the size of the bladder cavity. No tumour tissue was seen on the peritoneal surface of the bladder.

Microscopical.—Although several sections were examined, it was not possible to make out the bladder

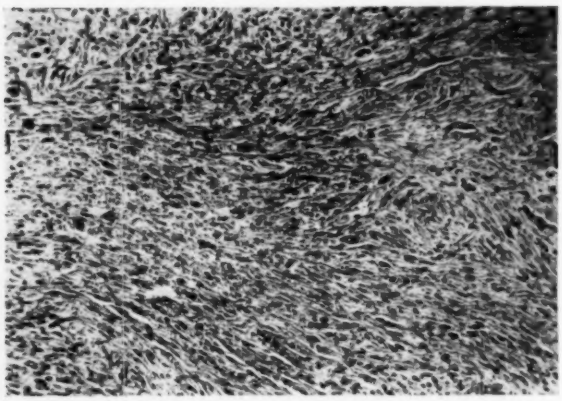

FIG. 549.—Low-power view, showing fusiform appearance of tumour cells. (H. and E.) (× 70.)

mucosa, which had undergone necrosis. The tumour cells were fusiform in appearance (*Fig.* 549) and showed marked variation in size and shape. The nuclei were large and hyperchromatic, a characteristic feature being the presence of a large number of tumour giant cells (*Fig.* 550). Mitoses were frequent.

DISCUSSION

The diagnosis of a bladder neoplasm was made on cystoscopic examination. Although the precise nature of the tumour was not known at this time, the extensive involvement of the bladder by the growth indicated that nothing short of complete cystectomy after ureteric transplantation would have sufficed in this case.

References to the literature already quoted show that, as regards local infiltration and metastases, bladder sarcoma shows a marked variation. Although the type of neoplasm can only be revealed by a microscopical examination, there does not appear to be any correlation between histological appearances and behaviour of the tumour. In the present case the histological features, e.g., presence of mitoses and cellular pleomorphism, suggested a highly malignant type with invasive characters. Yet the neoplasm was found to be confined to the bladder, its direction of growth being entirely towards the bladder cavity. The prognosis, too, in this case appears to be good, as the whole of the tumour-bearing area has been removed and as the patient is alive and well, with no evidence of recurrence or metastases, nearly two years after the operation.

SUMMARY

A case of leiomyosarcoma of the bladder in a female aged 32 years treated by total cystectomy after ureteric transplantation, is reported. The patient is alive and well and free from recurrence or metastases nearly two years after operation.

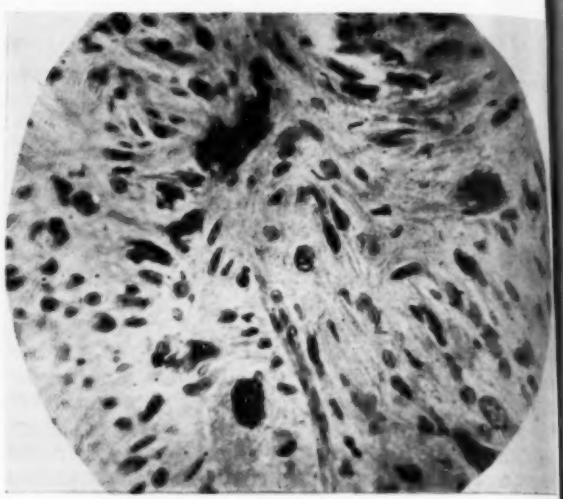

FIG. 550.—High-power view showing three tumour giant cells. (H. and E.) (× 200.)

References to literature indicate a marked variability in the behaviour of bladder sarcoma. Histology is of value only in determining the type of tumour, but does not help in the prognosis.

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A CASE OF CYSTOSARCOMA PHYLLODES

By ARCHIBALD L. GOODALL and ROBERT C. CURRAN

FROM THE UNIVERSITY DEPARTMENTS OF SURGERY AND PATHOLOGY, ROYAL INFIRMARY, GLASGOW

In the *Edinburgh Medical and Surgical Journal* of April, 1827, there appeared a paper by William Cumin on "A General View of the Diseases of the Mamma". The manuscript is preserved in the Library of the Royal Faculty of Physicians and Surgeons. This paper included a case-history which forms the earliest detailed description of the lesion later called "cytosarcoma phyllodes" by Johannes Müller (1838). Cumin's accurate and careful description merits reproduction in full :—

"Mrs. McD., aged 24, admitted into the Glasgow Royal Infirmary on November 14, 1818. Five years ago, without any known cause, a small tumour began to form in the centre of the left mamma. It was occasionally affected with lancinating pain, which became more severe at the menstrual periods. The tumour of the mamma appears now to be composed of several smaller ones, which are connected to one another. They feel hard and somewhat irregular on their surface, and each is about the size of an orange ; the whole forming a very weighty mass, as large as a child's head. It is free from pain, even when handled, is movable on the subjacent parts, and does not adhere to the skin, which is of its natural colour ; but the superficial veins of the breast are extremely turgid. In the axilla is an enlarged gland, which has always been free from pain. Health good ; functions natural. She is now in the sixth month of pregnancy and she has had three children since the complaint commenced.

"On the November 17, the whole tumour was removed, along with several enlarged axillary glands, which did not appear otherwise diseased. The tumour consisted of a number of smaller ones, with a cavity in the centre filled with serous fluid, into which many of the tumours projected . . . the solid portion of the tumour and the skin covering it weighed 57½ ounces.

"The case of Mrs. McD. corresponds exactly with the description given by Sir Astley Cooper of what he has named 'encysted tumour of the mamma'. He considers it is always of a benign character and never liable to return after extirpation. Of the truth of the latter part of the opinion, I am well convinced." The woman was alive and well eight years later.

FIG 551.—Macroscopical appearance of the tumour, showing the very large fungating ulcer.

CASE REPORT

The specimen which forms the basis for this article was from Mrs. G., aged 64, who was referred to one of us (A. L. G.) in June, 1950, complaining of a large ulcerating tumour of the left breast. She was a widow and her last child had been born twenty-nine years before. No previous breast disease was reported and she had fed her three children without difficulty. Three years before she had noticed a small tumour of the left breast. This rapidly increased in size and, after eighteen months, the skin broke down and ulceration commenced. Large sloughs and blood-clots were discharged and there was a foul stench. Bleeding was easily provoked.

Owing to domestic conditions, the patient did not consult a doctor and continued to dress the large ulcer for eighteen months. There was no loss of appetite or weight and there was no systemic upset.

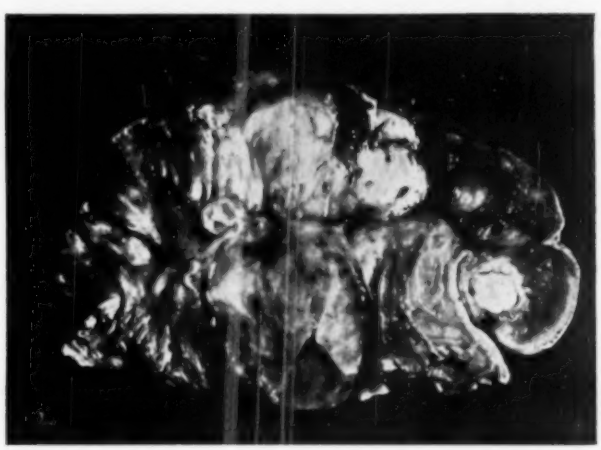

FIG. 552.—Tumour bisected to show the lobulated architecture. The tumour projects a considerable distance beyond the skin margin, easily visible in the right side of the specimen. (× ¼.)

On examination the patient was slightly anæmic (Hb 10 g. per 100 c.c.) but in good health apart from the lesion of the breast. The right breast was normal.

The lower two-thirds of the left breast was replaced by a large soft tumour with a sharply defined upper margin (*Fig.* 551). Over the tumour an area of ulceration 20 × 15 cm. had occurred, revealing a foul surface which discharged large sloughs and bled on slight touch. No glands were felt in the axilla.

On June 10, under pentothal and cyclopropane anæsthesia, local removal of the left breast with the pectoral fascia was carried out. Owing to sclerosis of the vessels, bleeding was rather free and one pint of blood was transfused. There was some difficulty in closing the wound and, in spite of prophylactic penicillin, mild infection occurred.

Further progress was uneventful and the wound healed soundly. When last heard of a year later, she was well and leading an active life which included driving a car.

PATHOLOGY.—The breast was largely replaced by a large fungating tumour (weight 1800 g.) which projected 7 cm. above the skin surface as a dark-red necrotic ulcer measuring 20 × 15 cm. The nipple could not be identified. The surrounding skin appeared normal.

When bisected, the neoplasm had a dark grey translucent appearance and the most remarkable feature was its lobulated architecture (*Fig.* 552). It consisted of numerous lobes like broad leaves, mutually compressed and apparently arising from a common stem. Probably, the tumour could best be described as of cauliflower structure.

Microscopically, the tumour is a fibro-adenoma mainly of intracanalicular type, with large intra-acinar projections.

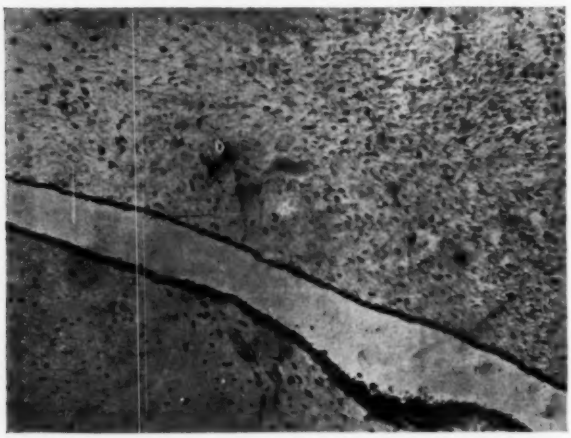

FIG. 553.—Microscopical appearance of the tumour, showing the myxomatous nature of the large intra-canalicular projections. (Heidenhain's iron hæmatoxylin.) (× 75.)

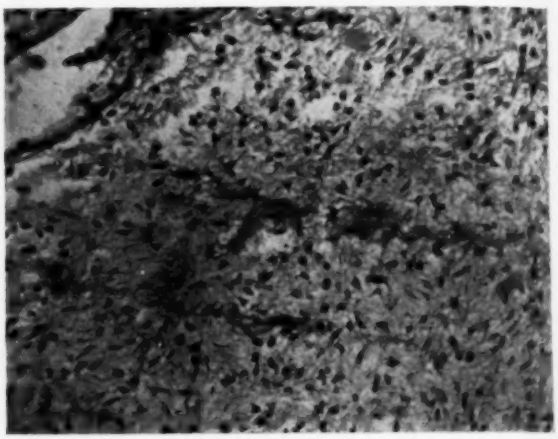

FIG. 554.—Relatively cellular area of the fibrous component of the tumour. Slight cellular pleomorphism is present, but mitotic figures are not evident. (H. and E.) (× 150.)

In the adenomatous portion many of the ductules appear to be lined by double layers of cells, but the basement membranes are well preserved and there are no aberrant cells. The fibrous component is unduly preponderant and, though varying considerably in density, is remarkably acellular and myxomatous. It fails, however, to stain for mucin or with the periodic acid-Schiff method. Mitotic figures are absent and the myxomatous tissue presents a remarkably uniform appearance. Thus, according to the usual cytological criteria, the growth is not malignant (*Figs.* 553, 554).

DISCUSSION

This type of giant fibro-adenoma having a phyllodes structure is uncommon.

Lee and Pack (1931, a, b) published 109 cases collected from the literature. Their list includes Cumin's case (*see above*), but omits a probable specimen weighing 16 lb. described by John Hunter (1835). Owens and Adams (1941) added 12 cases and *Table I* catalogues cases published since that date together with some which previous authors had omitted. We do not claim that this is a complete list, as undoubtedly some specimens masquerade under different names and it includes cases of giant fibro-adenomata not clearly stated to be of phyllodes type.

Typical examples of cystosarcoma phyllodes are of 'cauliflower' structure. This analogy must not be carried too far, but it serves to emphasize the essential architecture of the neoplasms quite apart from their size. The tumours are fibro-adenomata and the 'lobes' of the cauliflower correspond to large intracanalicular projections of myxomatous tissue. These projections of gelatinous material abut on one another, causing mutual compression, yet remain separated by slits which occasionally are relatively large and cystic. As no histological examination was made on the earliest published cases, Müller's term 'sarcoma' no doubt derived from the main clinical features of the tumours, in particular their relatively rapid growth, their large and even enormous size, and the frequency of extensive skin ulceration. These suggested malignancy, but Müller recognized that the post-operative prognosis was good, and though subsequent writers have accepted Müller's designation, the innocent nature of the tumour has been tacitly acknowledged. On this account, Lee and Pack (1931, b) and Owens and Adams (1941) suggested that the term 'cystosarcoma' be discontinued, but it must be recognized that frankly malignant variants occur (White, 1940). Cooper and Ackerman (1943) had a case which recurred as a cellular sarcoma with lymph-gland metastases. Geschickter (1945) reported 9 fibrosarcomata in 49 cases of giant fibro-adenomata, but the significance of this observation is vitiated by the absence of specific details of the tumours. Several other authors, e.g., Hinterberger (1942), Fox, Castellano, and Gimenez (1944), Funck-Brentano, Bertrand, and Poilleux (1938), Mazzetti (1947), have described cases in which clinical or microscopical features implied sarcomatous transformation, and Harrington and Miller (1940), in their article on sarcomatous and carcinomatous change in fibro-adenomata, included 2 cases (II and III) of 'adenofibrosarcomata' which conform to our conception of 'cystosarcoma phyllodes'. Hill and Stout (1942), discussing sarcoma of the breast, state that sarcomatous change in fibro-adenomata of intracanalicular type constitutes the form commonly called 'cystosarcoma phyllodes'. They recorded 14 cases of this type—one, apparently, a pericanalicular fibro-adenoma of giant size—and all survived for long periods. Brachetto-Brian (1949) gave an account of 14 cases of sarcoma of the female breast. Four of these were of phyllodes nature, but were not differentiated on this account from the remainder. He maintained from his study that breast sarcoma is of low malignancy and that radical operation offers a reasonable prospect of cure. Fitzwilliams (1924) wrote of and illustrated a large intracanalicular fibro-adenoma "undergoing sarcomatous degeneration".

Table I

No.	Author	Age	Sex and Marital State	Parity	Relation to Pregnancy and Lactation	Trauma	Location	Skin of Breast	Precursory Tumour	Rate of Growth	Duration	Size	Chief Physical F Sympto
1	Hunter (1835)	38	F.	—	—	—	—	Ulcerated	—	—	12 yr.	16/18 lb.	—
2	Paget (1853)	Described three cases in sisters. Two of these were huge myxomatous tumours and the third was called 'fungoid disease'						One ulcerated	—	—	—	—	—
3	Creighton (1902)	—	F.	—	—	—	—	—	—	—	—	—	—
4	Fujita and Kishi (1939)	14	F.	—	After puberty	—	R. and L.	Not ulcerated	—	R.	1 yr., 6 mth.	'Huge'	Huge bilateral mamma no upset in health
5	White (1940)	34	F., S.	—	—	—	L.	*Peau d'orange* and atrophy in one area	Yes	S., R.	2 yr.	21 × 19 × 9 cm., 3781 g.	Size troublesome. lobulated. Recurren 1 yr., 7 mth.
6	Hinterberger (1942)	32	F., M.	—	Pregnant	—	R.	Not ulcerated	Yes	R.	2 mth.	Size of apple	Recurrent tumours (6
7	Reed and Hiebert (1942)	18	F.	—	Pregnant	—	R. and L.	R. ulcerated; L. imminent	Yes	S., R.	3 yr.	R. 11 cm., L. 12 × 12 × 5 cm.	Great enlargement d Operation after deliv
8	Althabe et al. (1942)	45	F., M.	—	—	—	L.	Skin congested, veins engorged	Yes	S.	—	Adult head, 1800 g.	Firm nodular tumour
9	Hill and Stout (1942)	33–69	F.	—	—	—	—	—	—	S., R.	Average 1 yr., 6 mth.	3½ cm./15 lb.	15 cases are describe sarcoma
10	Cooper and Ackerman (1943)	57	F., M.	—	—	—	L.	Ulcerated	Yes	S., R.	3 yr., 5 mth.	21 × 20 cm., 1940 g.	Large ulcerated mass
11	Cooper and Ackerman (1943)	75	F., M.	—	—	—	R.	—	Yes	S., R.	10 yr.	15 × 15 cm., 1130 g.	Large drop-shaped m No glands
12	Cooper and Ackerman (1943)	51	F., M.	—	—	—	L.	—	Yes	S., R.	12 yr.	1750 g.	Large, soft, nodular t
13	Fox et al. (1944)	15	F., S.	—	—	—	L.	Skin thin and glistening	—	S.	8 mth.	Fœtal head	No systemic upset. normal
14	Fox et al. (1944)	50	F., M.	2	—	—	R.	—	Yes	S.	2 yr.	Large orange	Hard tumour, no glan retracted
15	Giglioli (1946)	32	F., M.	—	—	—	L.	Shiny, but not fixed to tumour	Yes	S., R.	10 yr.	Baby's head, 1370 g.	Size troublesome, no
16	Malbec (1946)	—	F.	—	—	—	L.	Not ulcerated	—	S., R.	—	—	Size troublesome, no
17	Mazzetti (1947)	47	F., M.	—	—	—	R.	Ulcerated	—	R.	2 yr.	4100 g.	Size troublesome, so ulceration. No glan
18	Mosconi (1947)	64	F., M.	5	—	—	L.	Skin tense and shiny; *peau d'orange*	Yes	S., R.	15 yr.	Adult head, 7250 g.	Pain from weight, present
19	Clarke (1948)	52	F., M.	—	—	—	R.	Ulcerated	—	S.	13 yr.	6 × 9 × 10 in., 10 lb.	Pedunculated tumour
20	Santy et al. (1948)	68	F.	—	—	—	L.	Ulcerated	Yes	S., R.	8 yr.	Adult head, 2700 g.	Ulcerated tumour. N
21	Willis (1948)	77	F., M.	—	—	—	L.	Inflamed and ulcerated	—	S.	40 yr.	25 cm., 9 lb.	Hemispherical, tense
22	Willis (1948)	45	F., M.	Multi.	—	Severe blow 7 mth. before	L.	—	—	R.	5 mth.	13 cm., 1350 g.	Well-defined rounde
23	Willis (1948)	40	F., M.	—	—	—	—	—	Yes	S., R.	—	10 cm.	Well-defined rounde
24	Horton and Baker (1950)	48	F., M.	—	—	Yes	L.	Red, stretched, and shiny	—	R.	4 mth.	Colossal, 6960 g.	Enormous tumour, glands
25	Gerwig (1949)	40	F., M.	4	—	—	L.	Tight and shiny. Not attached	Yes	S., R.	11 yr.	30 × 15 × 20 cm., 7830 g.	Large tumour. Ul breast sling
26	Bolivar (1950)	26	F., M.	—	—	—	L.	Tight and purplish. Congested veins	Yes	S., R.	8 yr.	Fœtal head, 22 × 21 × 13 cm., 3450 g.	Large lobulated tum upset
27	Authors' case	64	F., M.	3	—	—	L.	Ulcerated	No	S.	3 yr.	20 × 15 × 7 cm., 1800 g.	Ulcerated tumour p skin. Little systemi

Illustrations of large mammary tumours which resemble cystosarcomata are included in Fitzwilliams (1924), Black (1950)

Table I

OF TH	DURATION	SIZE	CHIEF PHYSICAL FINDINGS AND SYMPTOMS	NOMENCLATURE	TREATMENT
	12 yr.	16/18 lb.	—	Scrofulous breast	Local mastectomy
	—	—	—	—	—
	—	—	—	Fibroma	—
	1 yr., 6 mth.	'Huge'	Huge bilateral mammary enlargement; no upset in health	Hyperplasia of puberty	Radical excision a plastic
.	2 yr.	21 × 19 × 9 cm., 3781 g.	Size troublesome. Huge, smooth, lobulated. Recurrence and death in 1 yr., 7 mth.	Cystosarcoma phyllodes	Local mastectomy
	2 mth.	Size of apple	Recurrent tumours (6) in 7 years	Sarcoma phyllodes lipomatodes mammæ	Local mastectomy
.	3 yr.	R. 11 cm., L. 12 × 12 × 5 cm.	Great enlargement during pregnancy. Operation after delivery	—	Local mastectomy
	—	Adult head, 1800 g.	Firm nodular tumour	Giant intracanalicular fibro-adenoma	Local mastectomy
.	Average 1 yr., 6 mth.	3½ cm./15 lb.	15 cases are described as adenofibrosarcoma	Adenofibrosarcoma	5 radical, 7 lo mastectomy, 3 lo removal
.	3 yr., 5 mth.	21 × 20 cm., 1940 g.	Large ulcerated mass	Cystosarcoma phyllodes	Local mastectomy
.	10 yr.	15 × 15 cm., 1130 g.	Large drop-shaped mass. No fixation. No glands	Cystosarcoma phyllodes	Local mastectomy
.	12 yr.	1750 g.	Large, soft, nodular tumour	Cystosarcoma phyllodes	Local removal; la radical
	8 mth.	Fœtal head	No systemic upset. No glands, nipple normal	Intracanalicular fibro-adenoma	Radical mastecto
	2 yr.	Large orange	Hard tumour, no glands, nipple slightly retracted	Tumour of phyllodes type	Radical mastecto
.	10 yr.	Baby's head, 1370 g.	Size troublesome, no systemic upset	Fibro-adenoma	Local mastectomy
.	—	—	Size troublesome, no glands	Fibro-adenoma	Removal and pla repair
	2 yr.	4100 g.	Size troublesome, some cachexia after ulceration. No glands	Sarcoma	Local mastectomy
.	15 yr.	Adult head, 7250 g.	Pain from weight, asthenia, glands present	Malignant degeneration of fibro-adenoma	Radical mastecto
	13 yr.	6 × 9 × 10 in., 10 lb.	Pedunculated tumour. Thyrotoxicosis	Adenofibroma	—
.	8 yr.	Adult head, 2700 g.	Ulcerated tumour. No glands	Adenoma of phyllodes type	Local mastectomy
	40 yr.	25 cm., 9 lb.	Hemispherical, tensely cystic tumour	Giant fibro-adenoma	Local mastectomy
	5 mth.	13 cm., 1350 g.	Well-defined rounded tumour	Giant fibro-adenoma	Radical mastecto
	—	10 cm.	Well-defined rounded tumour	Giant fibro-adenoma	Breast amputated
	4 mth.	Colossal, 6960 g.	Enormous tumour, no fixation, no glands	Cystosarcomatoid phyllodes	Radical mastecto
	11 yr.	30 × 15 × 20 cm., 7830 g.	Large tumour. Ulcer of neck from breast sling	Cystosarcoma phyllodes	Local mastectomy
	8 yr.	Fœtal head, 22 × 21 × 13 cm., 3450 g.	Large lobulated tumour. No systemic upset	Intracanalicular fibro-adenoma	Local, with pla repair
	3 yr.	20 × 15 × 7 cm., 1800 g.	Ulcerated tumour projecting from the skin. Little systemic upset	Cystosarcoma phyllodes	Local mastectomy

emble cystosarcomata are included in Fitzwilliams (1924), Black (1950), Copeland and Geschickter (1950), and Saner (1950).

REATMENT	GROSS PATHOLOGICAL ANATOMY	HISTOPATHOLOGY
mastectomy	—	—
—	—	—
—	Fibroma with large, irregular, cystic spaces. In places, of gelatinous chondriform character	Cystic sarcoma
l excision and ic	None given	Fibro-adenomata of both breasts
mastectomy	On section, much pale serous fluid escaped. Glistening, with narrow clefts separating lobules	Much debate; four experienced pathologists diagnosed cystosarcoma phyllodes eventually
mastectomy	Tumours varied in size; largest, size of an orange	Microscopically, diagnosis varied from cellular fibroma (? sarcoma) to sarcoma phyllodes (later in series)
mastectomy	R., circumscribed necrotic mass and smaller tumour. L., two masses, 5 × 3 cm., with cysts	R., fibro-adenomata with inflammation and necrosis in lactating breast. L., similar picture but with less necrosis
mastectomy	'Cauliflower' on section with a cystic part. Greyish cut surface	Fibro-adenoma with areas of necrosis and cystic change
lical, 7 local ectomy, 3 local val	14 cases correspond to cystosarcoma phyllodes	10 intracanalicular fibro-adenomata; 2 mixed fibro-adenomata; 2 undetermined; 1 pericanalicular fibro-adenoma
mastectomy	Tumour made up of various sized nodules with clefts and lacunæ between them	Early connective-tissue proliferation of intracanalicular type
mastectomy	Tumour made up of nodules with clefts and lacunæ between	Connective-tissue proliferation with areas of myxoma-like stroma
removal; later al	Tumour made up of nodules with clefts and lacunæ between	Family physician excised primary tumour (cystosarcoma phyllodes). Recurred and metastasized as cellular sarcoma
l mastectomy	Tumour encapsulated, lobulated and nodular	Intracanalicular fibro-adenoma with hyperplastic epithelium
l mastectomy	Large tumour with 'cauliflower' appearance	Fibro-adenoma; appearance of stroma suggests sarcomatous change
mastectomy	Lobulated and nodular; whitish, 'cauliflower' appearance. One cyst 50 c.c.	Fibro-adenomata of intracanalicular type in both breasts
val and plastic ir	—	Fibro-adenoma
mastectomy	Firm and fibrous with ulcer covered with clot. No glands, no lobulation	Sclerotic fibro-adenoma of breast
al mastectomy	Irregular consistence; lobulated phyllodes structure. Greyish-pink, hæmorrhagic. One large cyst	Intracanalicular fibro-adenoma with no evidence of sarcoma
—	Tumour composed of yellowish-grey soft fibrous nodules	Intracanalicular and pericanalicular fibro-adenomata
mastectomy	Refer to original article. Five cases in all	"Aspect de conjonctivome benin. Cellules sans mitoses. Pas de necrobioses. Aspect myxoide en certains points"
mastectomy	—	Simple fibro-adenoma, mainly pericanalicular, with abundant acellular connective tissue
al mastectomy	Soft œdematous fibro-adenoma	Mixed fibro-adenoma, mainly intracanalicular. Cellular connective tissue. Fusiform cells. Many mitoses
t amputated	Soft fibro-adenoma	Mixed fibro-adenoma, equally peri- and intracanalicular. Moderately cellular. Some mitoses
al mastectomy	White, opalescent, bluish, fibromyxomatous; recent hæmorrhage and multiple spaces	Cystic and œdematous adeno-myxofibroma (cystosarcoma phyllodes)
l mastectomy	Firm, irregular tumour of breast, like 'bag of oranges'. No glands	Tumour largely myxomatous, mitoses absent (cystosarcoma phyllodes)
l, with plastic ir	Lobulated tumour, variable consistence. Some parts fluctuant, some calcified. Deep clefts, no glands	Intracanalicular fibro-adenoma with œdematous, cellular, dense connective tissue. Variable activity of epithelium. Necrosis in parts
l mastectomy	Lobes of gelatinous or fibrous consistence projecting from ulcer. Greyish-pink. No glands	Intracanalicular fibro-adenoma with large intracanalicular processes. Myxomatous. No mitotic figures seen

Table I

In our opinion, in any assessment of the benignity of cystosarcoma phyllodes, the writings of these more recent authors must not be ignored.

Table I provides a convenient indication of the age, sex, marital state, parity, and pregnancy of the patients. Repeated births and lactations undoubtedly may be potent factors in converting small fibro-adenomata into large ones and even into cystosarcoma phyllodes; the effect of pregnancy alone in causing an increased rate of growth is seen strikingly in the cases of Cumin (1827) and of Reed and Hiebert (1942). The patient frequently has a symptomless precursory tumour which, after remaining constant in size for several years, rapidly enlarges. The proximate cause of this rapid enlargement is unknown. Lee and Pack (1931, b) suggested that trauma may be a factor in accelerating growth, if not initiating it.

Several clinical points should be stressed: The skin of the breast may be ulcerated, and is almost invariably so in the largest specimens. Indeed, ulceration is often the factor which leads these women to seek advice. The lobes of the tumour may project from the wound noticeably, as in our present case and in that impressively illustrated by Mannix and Wildnauer (1949). It is important to note that ulceration is due to rupture of rather than to invasion of the skin.

It is probable that the tumours arise in fibro-adenomata and that the increased rate of growth coincides with the myxomatous transformation of the fibrous component. Willis (1948) states that most prominently myxomatous tumours are to be regarded as malignant and that attempts to distinguish between myxoma and myxosarcoma are futile. In view of the fact that the main connective-tissue component of the cystosarcoma phyllodes is myxomatous, we advocate the terminological separation of cystosarcoma from fibro-adenoma. Lee and Pack (1931, b) suggested the name 'giant myxoma', but in our opinion there is much to be said for the retention of the older, if more ominous, designation of cystosarcoma phyllodes.

SUMMARY

A case of cystosarcoma phyllodes (giant intracanalicular fibro-adenoma) is presented, with a review of the recent literature. The main features of this comparatively rare tumour are discussed and a plea made for Müller's term of 'cystosarcoma phyllodes'.

Addendum.—Since this paper was submitted for publication, two large series have been reported, 77 cases by Treves and Sunderland (1951) and 9 cases by McLaren (1952). The criteria of these authors have allowed the inclusion of many cases which we would not include in the term cystosarcoma phyllodes.

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INTRACAPSULAR FRACTURES OF THE NECK OF THE FEMUR
A REVIEW OF ONE HUNDRED CASES TREATED BY INTERNAL FIXATION

By MARK L. MASON

SENIOR ORTHOPÆDIC REGISTRAR, SOUTH EAST KENT, CANTERBURY, AND ISLE OF THANET GROUPS OF HOSPITALS
LATE SENIOR REGISTRAR, ORTHOPÆDIC DEPARTMENT, WEST LONDON HOSPITAL, HAMMERSMITH

THE treatment of the fracture of the femoral neck was revolutionized with the introduction by Smith-Petersen in 1931 of the three-flanged nail for internal fixation.

The problem of the usually aged patient with such a catastrophic injury had been a source of great trial and perplexity to the surgeon for many surgical eras, and had been called " the unsolved fracture ". With this new method, great advances in the treatment and end-results were visualized, and there was hope that the burden of anxiety these patients constantly entailed would be significantly reduced.

Royal Whitman's (1925) method of reduction and immobilization had been accepted with alacrity as a major step forward, but the surgeon was still

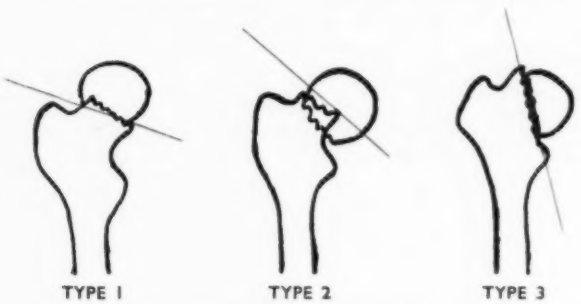

FIG. 555.—Pauwels' classification. Type 1, Impacted valgus; Type 2, Transcervical; Type 3, Subcapital.

perturbed by the initial and late mortality that such complete and prolonged immobilization inevitably brought.

Whitman himself claimed some 40 per cent of union of the fractured neck, provided the cases were carefully followed up. Before this, some 80 per cent of aged patients with such an injury died within three months of the initial trauma, and even in Whitman's plaster, pneumonia, plaster sores, and knee stiffness were difficult, if not impossible, to prevent.

The advantages of internal fixation for the fracture of the femoral neck are now well-established :

1. The fracture is immobilized.
2. The patient may become mobile, and pulmonary complications thereby avoided.
3. Plaster-of-Paris sores are non-existent, and bed-sores largely preventable.
4. Muscle atrophy can be minimized and knee stiffness avoided.
5. Nursing becomes easier and relatively painless.

The purpose of this report is to review 100 cases of fracture of the femoral neck treated by internal fixation, using the three-flanged nail; to follow up their activities; to evaluate their quality of life, and to compare it with that prior to the injury. The demands that the aged make on themselves grow less as they proceed in years, and they adapt their philosophy insidiously to cope with the natural 'infirmities' that old age brings. It was, therefore, found very difficult to create some standard on which to base an opinion as to whether a result could be considered good or indifferent.

Each patient reviewed, therefore, was assessed on his or her own merits, bearing in mind the lessened activity that five years may bring to a person of sixty-five, and the final assessment was made on function and quality of life only, irrespective of whether radiography showed a united fracture or examination revealed full range of movement. The proportion of unions and non-unions was, however, also recorded.

Classification.—Pauwels' (1935) classification (*Fig.* 555) of fractured femoral necks was used, and all cases under review fell into one or other of his three categories. There were 58 transcervical fractures, as opposed to 38 subcapital fractures in this series. There were 69 left femoral necks and 31 right femoral necks (*Table I*).

Age and Sex Incidence.—The average age of these patients was 69, the youngest being 26 and the

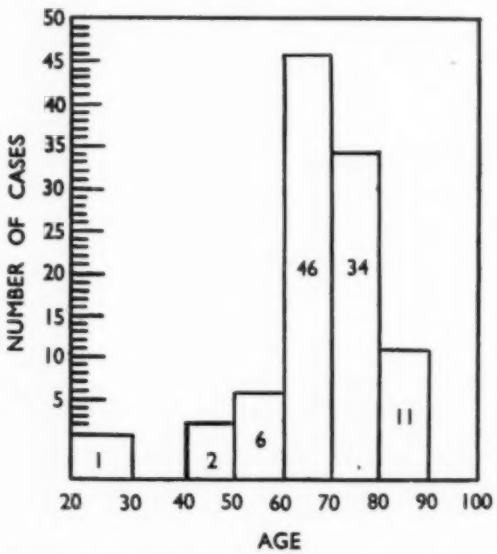

FIG. 556.—Age incidence of 100 fractured femoral necks, Males 9, females 91. (Average age, 69.)

eldest 90. The largest age group was between 60 and 80 (*Fig.* 556). There were 91 female patients and 9 male patients.

Method of Treatment.—All the cases under review were treated by internal fixation, using a three-flanged pin. The treatment was undertaken by four surgeons, but the essential technique was the same. Thirty-nine (39 per cent) were treated by initial traction, using Kirschner wire skeletal traction, or skin traction in a Thomas' splint with 10 to 12 lb. weight for an average of 8 days

prior to operation. The longest period of traction was 25 days and the shortest was 2 days. During this period, assessment of the general condition was made, and any incidental condition treated if necessary. Sixty-one cases were immobilized in sand-bags for an average of 4 days prior to operation, the longest period being 18 days and the shortest being 1 day. No pinning was undertaken as an emergency. The 'closed' method under general anæsthesia was employed, using a lateral incision, guide wire, and X-ray control in both anteroposterior and lateral views.

Table I.—Classification of 100 Fractured Necks of Femur

Type	*No. of Cases*
Impacted valgus	4
Transcervical	58
Subcapital	38
Number of left femurs	69
Number of right femurs	31

Post-operative Care.—Various methods were used to prevent the affected leg from falling into external rotation. Physiotherapy was commenced immediately, and generally, the patient was allowed out of bed as soon as possible after the wound had healed and the sutures had been removed.

Table II.—Deaths as a Result of Injury and/or Operation (Average Age—78 Years)

Case	Age	Time after Operation	Place of Death	Cause of Death
S.P.	84	Four months	Home	Myocardial failure, bed-sores *
J.P.	83	Three months	Home	Hypostatic pneumonia *
A.E.	78	Ten days	Hospital	Pulmonary embolus †
S.E.	78	Ten days	Hospital	Pulmonary embolus †
D.K.	65	Two months	Home	Cause unknown, but bedridden *
C.E.	80	Three months	Home	Myocardial failure, broncho-pneumonia *
A.H.	79	Four months	Home	Pneumonia, bed-sores *
H.B.	76	Two months	Home	Pneumonia, bed-sores *
E.S.	78	Two Months	Home	Broncho-pneumonia, bed-sores *

* Bedridden after operation;
† Confirmed post mortem.

Full weight-bearing was allowed on an average of 15 weeks after operation. This represents only the 'official' time before full weight-bearing was allowed, as most elderly patients have great difficulty in getting about non-weight-bearing on crutches, and invariably take some weight on their injured side.

Mortality.—There were 9 deaths in this series, 2 immediate, and 7 remote, but all were deemed related to the injury and/or operation. The average age of these patients was 78 years. Two died of pulmonary embolism, confirmed by post-mortem examination, and a combination of bed-sores and/or pneumonia accounted for most of the others (*Table II*).

SURVEY

Each of the 91 survivors was interviewed, their activities assessed, their function recorded, and an X-ray examination of the appropriate hip-joint taken. Of the 100 cases, 90 were assessed on their own statements as having had normal activities prior to the accident. One had limited activities before the fracture on account of rheumatoid arthritis. Investigation revealed that the 9 patients who died were deemed to have normal activities prior to the accident. The average length of time that had elapsed between operation and review was 25 months, the shortest being 10 months, the longest being 84 months.

Gait and Range of Movement.—Of the surviving 91 patients:—

48 (53 per cent) showed a normal gait, whilst
39 (43 per cent) patients had some degree of dip associated with ½–2 in. of shortening.
32 patients used no aid to their walking whilst
55 patients needed some form of support:—
- 40 patients used one stick,
- 6 patients used two sticks,
- 7 patients used crutches,
- 2 patients were fitted with a weight-relieving calliper.

The remaining 4 patients were bedridden.

The use of one stick was allowed as 'normal', as it was felt that with advancing years many of these patients would find the need of some support whilst ambulant, even had no injury befallen them.

Range of Hip Movement (*Table III*).—Hip function is a difficult assessment to make in the aged, and the range was evaluated as:—

Full if it were similar to the contralateral side or if there was no fixed deformity and the range was restricted by no more than 10° in any direction;

Table III.—Functional Result in 91 Survivors

Range of Hip Movement	*No. of Cases*
Full i.e. (1) If as the contralateral side, or (2) If no fixed deformity and was restricted by no more than 10° in any direction.	32*
Fair If fixed flexion or external rotation deformity not more than 10° and range of any movement was restricted by no more than 20°.	32*
Poor	23
Not recorded	4†

* 64 patients (70 per cent) had good hip function.
† Examination impossible on account of pain and senility. Patients were bedridden.

Fair if the fixed flexion or external rotation deformity was not more than 10°, and the range of movement was restricted by no more than 20° in any direction, or

Poor.

It will be seen that 64 patients (70 per cent) showed good hip range; 4 patients did not have their range recorded.

Range of Knee Movement (*Table IV*).—This was considered :—

Full if it were similar to the other side ;

Fair if it showed a range of 180°–90° or better, but less than full ;

Poor if less than 180°–90°.

A total of 63 patients (70 per cent) showed a knee range of 180°–90° or better. Four were not recorded.

Table IV.—FUNCTIONAL RESULT IN 91 SURVIVORS

Range of Knee Movement	*No. of Cases*
Full	28*
Fair 180°–90° or better (but less than full)	35*
Poor Less than 180°–90°	24
Not recorded	4†

* 63 patients (70 per cent) had good knee range.
† Examination impossible on account of pain and senility. Patients were bedridden.

Assessment of Pain (*Table V*).—Pain was the most difficult symptom to estimate objectively. Pain in the hip and knee were assessed together, and indirect questioning as to why a patient could not comfortably perform a normal activity, often revealed pain as the cause, when direct questioning gave an equivocal reply.

Table V.—PAIN ASSESSMENT IN THE HIP AND KNEE OF THE 'PINNED FEMUR' LIMB IN 91 SURVIVORS

Assessment	*No. of Cases*		*Percentage*
None	41		
		59 =	65*
Minimal : No interference with activities	18		
Moderate : Interfering with activities so as to limit them	21		23
Severe : Incapacitating	7		7
Not recorded	4		5

* 59 patients (65 per cent) had no handicap on account of pain.

Pain was assessed as :—

None ;

Minimal if there was no interference with activity or function ;

Moderate if the pain so interfered as to limit activity and function ;

Severe if the pain was incapacitating.

Fifty-nine patients (65 per cent) of the 91 survivors had no handicap on account of pain ; 28 patients (30 per cent) had sufficient pain to lessen the quality of their lives.

Radiological Examination.—Each patient had an anteroposterior and a lateral view taken of the affected hip, and the results are recorded as in *Table VI*. Fifty-three cases (58 per cent) showed X-ray evidence of union ; 38 cases (42 per cent) showed X-ray evidence of non-union. Avascular phenomena affecting the head and/or neck of the femur as seen on the X-ray film were also recorded, but union or non-union was the criterion of X-ray result. This recording is only an X-ray finding and was used only in conjunction with the final functional assessment. Many cases of X-ray union still proved to give a poor final result as will be shown below.

It is of interest to record that in all the 91 cases, X-ray evidence of gross osteo-arthritis was lacking, the joint space was slightly narrowed in most, but osteophytic outgrowths were small. The bone texture was usually rarefied, and there was little cyst formation in either the head of the femur or the acetabulum.

Table VI.—RESULT OF X-RAY EXAMINATION IN 91 SURVIVING PATIENTS

	No. of Cases	*Percentage of 91 Survivors*
Union	53	58
Non-union	38	42
Avascular necrosis of head	21*	
Neck absorption	29†	

* Avascular necrosis accounted for 21 failures (as regards function) but since only definite density of the head was recorded this figure of 21 in above table is probably too low.
† Absorption of the neck was no bar to union (i.e., was minimal) in 18 cases. It accounted for or was a result of non-union in 11 cases.

Assessment of Activity and Final Grading (*Table VII*).—The assessment of activity was made using the pre-injury activity of each patient as a standard. It was found, as was expected, that the presence or absence of pain in the limb played the most important part in the loss or gain of functional activity, and the final grading was built on a combination of pain and activity only, and was considered as :—

Grade A (good result) if pain was absent or minimal and activities judged as *normal* ;

Grade B (fair result) if pain was minimal or moderate, but with *limited* activity ;

Grade C (poor result) if the pain was severe and the patient *chair-* or *bedridden*.

Forty-nine cases (54 per cent) of the survivors had regained their pre-accident activities, whilst the remaining 42 (46 per cent) led a quality of life which was considerably poorer than their pre-injury state.

Table VII.—FINAL ASSESSMENT IN 91 SURVIVING PATIENTS TREATED BY INTERNAL FIXATION FOR FRACTURE OF THE FEMORAL NECK

Assessment	*No. of Cases*	*Percentage*
Grade A (good result)	49	54
Grade B (fair result)	23	26
Grade C (poor result)	19	20

This means that less than 50 per cent of the total patients in this series had been restored to their normal condition.

It was decided to analyse in detail the cases in these three groups, and tabulate these findings along with pain, range of movement, and X-ray appearances. *Table VIII* shows this analysis.

It will be seen that of the 49 patients classified as Grade A (good result) all had normal activity (one patient with rheumatoid arthritis classified as 'limited' having regained her normal pre-injury function).

Pain was none or minimal in all.

Hip range was good in all save 3 cases, but 9 cases showed a knee range of less than 180°–90°. X-ray evidence of union was present in 37 of these 49 patients, whilst 12 patients had non-union. Thus, only 41 per cent of the surviving 91 patients had both normal activity with union of the fracture, whilst 13 per cent of the survivors had normal activities and non-union of the fracture.

Twenty-three patients classified as Grade B (fair result) showed limited activity and were leading a quality of life below their pre-injury standard.

Sixteen cases complained of moderate pain, and 10 showed a poor hip range.

X-ray examination showed evidence of bony union in 11 of these patients and non-union in 12. Pain, therefore, was responsible in a large measure for the reduction in activity of this group.

Of the 19 patients classified as Grade C (poor result) 15 were chair-ridden, and could just stand or walk round their bed, spending most of the day in a wheel-chair, and 4 were permanently bedridden.

Seven patients complained of severe pain, whilst the range of hip and knee movement was poor in all but one patient who had full hip range.

X rays showed evidence of union in 5 cases, and non-union in 14 cases.

Pain again was a great incapacitating factor.

Table VIII.—Detailed Analysis of Activities; Pain; Range of Movement, and X-ray Appearances of 91 Survivors

	Grade A 49 Cases having regained Normal Activity	Grade B 23 Cases having regained Limited Activity	Grade C 19 Cases Chair- or Bedridden
Activities :			
Normal	48	—	—
Limited	1*	23	—
Chair-ridden	—	—	15
Bedridden	—	—	4
Not recorded	—	—	—
Pain : Hip and Knee			
None	36	2	3
Minimal	13	5	—
Moderate	—	16	5
Severe	—	—	7
Not recorded	—	—	4
Range of Movement			
Hip :			
Full	28	3	1
Fair	18	10	4
Poor	3	10	10
Not recorded	—	—	4
Knee :			
Full	23	5	—
Fair	17	12	6
Poor	9	6	9
Not recorded	—	—	4
X-ray :			
Union	37†	11	5
Non-Union	12‡	12	14

* Had rheumatoid arthritis before fracture.
† 37 patients (i.e., 41 per cent of the survivors) had regained normal activity and showed X-ray evidence of union.
‡ 12 patients (i.e., 13 per cent of the survivors) had regained normal activity and showed X-ray evidence of non-union.

DISCUSSION

This review demonstrates that every second patient undergoing a pinning operation for fracture of the femoral neck is doomed to have limitation of functional activity, and in consequence a lowered quality of life. The reason for failure is not always due to non-union. In this series, 12 cases of non-union regained full activity, whilst 16 cases of union had limited or poor activity.

Avascular phenomena affecting the head and/or neck of the femur is largely outside the control of the operating surgeon, and in this series accounted for twenty-one failures as regards function. This estimate is probably far too low, as only cases showing definite avascular necrosis were recorded, and undoubtedly the percentage would show an increase if a further follow-up of cases was made at a later date.

Many attempts have been made to eliminate this phenomenon and Venable and Stuck (1946) introduced a muscle flap in order to effect increase of the blood-supply to the neck and head of the femur, but too few cases have been described to evaluate its effect accurately. The immobilization secured by a trifin nail prevents further damage to the surviving untraumatized vessels, and Engel and May (quoted by Lewis, 1943) showed that new blood-vessels form along the pin tract and may improve the blood-supply to the head.

It would seem, therefore, that in order to secure the best possible blood-supply, complete reduction and immobilization is required if the vessels left intact after the initial trauma are to get the best possible

chance of continued existence and freedom from thrombosis.

Some surgeons argue, therefore, that as soon as possible after the trauma, reduction by traction in a Thomas splint should be undertaken in order to preserve the existing intact vessels to the head and neck of the femur.

Nebb and McLaughlin (1948) have shown, however, in a series of open reductions for subcapital fractures necessitating much stripping down of soft tissue, and consequent damage to the surviving blood-vessels, that, in fact, their percentage of unions was greater than in those treated by closed pinning.

In this present series, of the 39 cases (including 4 deaths) treated by initial traction-reduction, 18 cases (48 per cent) showed X-ray evidence of union. Of the 61 cases (including 5 deaths) treated by immobilization in sand-bags, 35 cases (47 per cent) showed evidence of union, there being, therefore, no appreciable difference in the ultimate result when assessed as union by X-ray examination.

The Fracture Committee of the American Academy of Orthopædic Surgeons reviewed, in 1939, 1485 cases of fractured femoral neck treated by Smith-Petersen pin. In the statistical report (Statistical Report, 1939) 89·4 per cent of unions was recorded and the mortality figure was 8·5 per cent. No account is given of the actual functional results.

In 1941 the same Committee reviewed 144 cases and recorded some 70 per cent of bony unions in the follow-up. Eyre-Brook and Pridie (1941), in a comprehensive survey of 75 cases, estimate an overall bony union of 70 per cent, but this figure includes those patients deemed to have union as assessed on good function. As has been shown in this report, however, good function does not necessarily mean bony union. Of the patients subjected to an X-ray examination they record a percentage bony union of 58·4, which supports the figures in this review, in which there were 58 per cent of unions of the surviving 91 patients as assessed by X-ray examination. The mortality-rate amongst patients of this series was 9 per cent, and 41 per cent of the survivors had regained both their pre-accident state and had X-ray evidence of union.

CONCLUSION

I believe this review represents a true cross-section of the average results of the pinning operation as generally performed. These results are humbling and discouraging. The fractured femoral neck well deserves its ill-gotten name, ' the unsolved fracture '. One fact, however, does emerge. Internal fixation of the fractured femoral neck with a three-flanged nail is a life-saving procedure with a mortality figure of only 9 per cent as compared with that of the pre-pinning era of 80 per cent. Age is no bar to operation, and expectation of life no consideration.

SUMMARY

1. A series of 100 fractured femoral necks treated by internal fixation with a three-flanged nail is presented. The functional activity is analysed in detail.

2. There were 9 deaths (9 per cent) and the 91 surviving patients were grouped according to activity and quality of life, and irrespective of X-ray findings or range of movement, into three categories :—

A. 49 (54 per cent) patients were classified Grade A (good result).

B. 23 (26 per cent) patients were classified Grade B (fair result).

C. 19 (20 per cent) patients were classified Grade C (poor result).

3. Less than 50 per cent, therefore, of the total patients in this review had regained their pre-injury activity. Of the group of 49 patients (classified Grade A), 37 showed X-ray evidence of union, whilst 12 had non-union.

Thus, 41 per cent of the surviving patients showed a return to pre-injury activity, *and union* of the fracture, whilst 13 per cent of the surviving patients showed a return to pre-injury activity, *and non-union* of the fracture.

4. Internal fixation of the fractured femoral neck is a life-saving procedure.

It is a pleasure to record my grateful thanks to the surgeons whose cases I reviewed, and to Mr. J. C. R. Hindenach for his constant encouragement. My special thanks to Miss Pamela Lawrence, clinical secretary, without whose help this review would not have been possible.

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CARCINOMA OF THE ŒSOPHAGUS WITH HISTOLOGICAL APPEARANCES SIMULATING A 'CARCINOSARCOMA'

By RODNEY SMITH and N. F. C. GOWING, London

The occurrence of a true carcinosarcoma is rare in human pathology and such a diagnosis should be made with caution. The possibility of the 'sarcomatous' element being merely an anaplastic component of the epithelial tumour must always be carefully excluded. Even where more specialized mesenchymal tissues such as bone and cartilage are present, the possibility of these having resulted from metaplasia in the non-neoplastic stroma must be considered. These points have been stressed by several authors (Trudhope and Chisholm, 1934; Willis, 1948).

Nevertheless, a few reported cases, such as the two tumours of the breast described by Govan (1945), appear to be genuine examples of carcinosarcoma. In Govan's cases the sarcomatous moiety appeared to be derived from striated muscle. A few cases of true mixed tumours have also been reported in the thyroid, but more commonly in dogs than in man (Rudduck and Willis, 1938).

Malignant obstruction of the œsophagus is now routinely treated when possible by œsophagectomy, and in examining the increasing numbers of excised tumours one should remain alive to the possibility of an epithelial tumour exhibiting, in this region as elsewhere, areas suggesting a tumour of mesenchymal origin. As in all surgery, it is useful to remember that unusual manifestations of common lesions are more often encountered than the classic manifestations of rare lesions. Sarcoma of the œsophagus is a very rare lesion and carcinosarcoma must be even rarer. The case to be described is one in which the latter tumour was simulated by a carcinoma presenting unusual histological features.

CASE REPORT

Mrs. M. M., aged 53, had been in good health until three months previously, when she had begun to have difficulty in swallowing solids. The dysphagia increased progressively and she was now having difficulty even with liquids. She had lost 2 st. in weight and also complained of lassitude and a recent cough which kept her awake at night.

Physical examination revealed a minute, wasted lady weighing 5½ st. Apart from the obvious loss of weight, examination provided merely negative evidence and there was no detectable secondary metastasis from the suspected carcinoma.

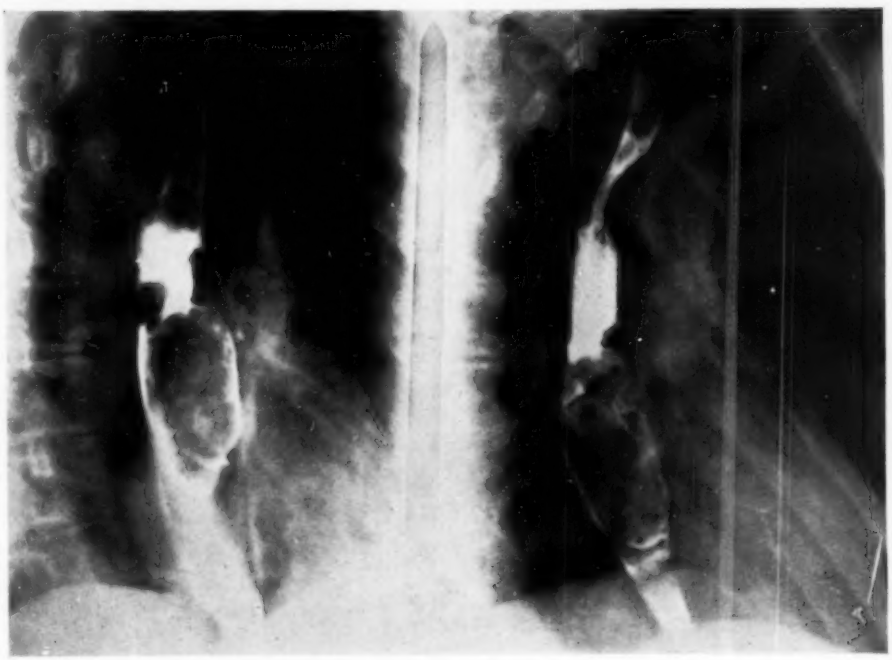

Fig. 557.—Pre-operative barium swallow.

Barium swallow (*Fig.* 557) showed a constant large filling defect, the œsophagus being expanded by an intraluminal tumour, and an area of stenosis directly above it.

Œsophagoscopy confirmed the presence of a friable tumour and the report on a piece taken for biopsy was: "Histological examination shows a poorly differentiated squamous-celled carcinoma".

Radiographs of the lungs and bronchoscopy revealed no abnormality. A mild secondary anæmia was corrected before operation, during which a slow drip transfusion of whole blood was maintained.

Anæsthesia was induced with pentothal and maintained with intratracheal nitrous oxide, oxygen, and cyclopropane, supplemented by curare.

At Operation.—A long incision was made following the sixth left interspace and posteriorly extending

upwards to the level of the third rib. The sixth interspace was opened into the pleural cavity and posteriorly, in order to gain adequate access, 1 in. of each of the fourth to the eighth ribs was excised. When the mediastinum

FIG. 558.—Post-operative barium swallow.

was entered and the tumour palpated, it was found to extend in its upper part to the lower margin of the arch of the aorta. It was, however, mobile, and it was considered that it could be removed in its entirety.

The diaphragm was now split radially from the hiatus and the peritoneal cavity opened. No intra-abdominal secondary deposits could be found. The stomach was extensively mobilized, dividing the lesser omentum, gastro-splenic ligament, and gastro-colic omentum, but preserving the right gastric and right gastro-epiploic vessels and the gastro-epiploic arcade.

The œsophagus was mobilized up to the arch of the aorta and, after incision of the pleura above the arch, completely mobilized behind the arch and above it to the level of the manubrium sterni. It was now divided just above the aortic arch and the whole of the œsophagus distal to this point removed together with the cardia of the stomach and adjacent lesser curvature with the left gastric group of lymph-glands.

The incision into the lumen of the stomach so made was closed and the fully mobilized viscus drawn up into the chest in front of the aortic arch, the fundus reaching beyond the cut proximal œsophagus without difficulty. It was anchored in this situation with a number of interrupted silk sutures to the parietal pleura, and the œsophagus, lying upon its anterior surface, was anastomosed to it by end-to-side anastomosis, the redundant stomach being wrapped around the anastomosis to enclose it completely. Interrupted silk sutures on eyeless needles were used throughout. The junction

and the exposed mediastinal cellular tissue were dusted with penicillin-sulphathiazole powder and the thorax closed with a rubber-tube drain inserted through a stab incision in the eighth interspace. This was later connected

FIG. 559.—Gross appearance of the tumour. (Natural size.)

to an under-water seal. The condition of the patient remained good throughout the operation.

PROGRESS.—Post-operatively, fluids were allowed by mouth after the first 24 hours and feeds increased until

FIG. 560.—Microscopical appearance of the tumour. Low power. (H. and E.) A, Anaplastic carcinoma cells lying in stroma and producing a 'sarcomatous' appearance; B, C, Groups of well-differentiated cancer cells.

soft solids were taken after ten days and a normal diet after three weeks. There was little drainage from the intercostal tube, which was removed after 48 hours.

Some patchy atelectasis on both sides resolved spontaneously without recourse to bronchoscopy. Convalescence was otherwise uneventful and the patient was discharged to a convalescent home after three and a half weeks. A post-operative barium swallow (*Fig.* 558) showed a normally functioning stoma.

She remained in good health for a little under three years, when recently renewed dysphagia occurred.

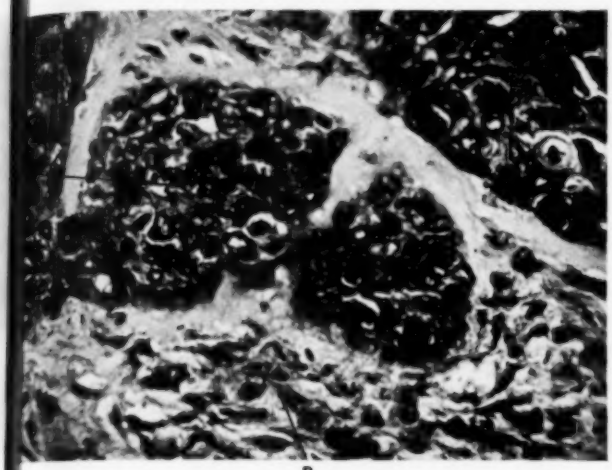

FIG. 561.—Microscopical appearance of the tumour. High power. (H. and E.) A, Compact group of well-differentiated cells; B, Loosely arranged anaplastic cells lying in stroma.

Investigation has now revealed recurrence of an anaplastic carcinoma in the œsophageal stump.

PATHOLOGICAL REPORT.—The report on the excised œsophagus was as follows:—

Macroscopical Appearance.—The tumour is roughly ovoid in shape, measuring 5·5 cm. in length and 2·5 cm. in its greatest diameter, tapering towards its lower extremity. It is attached to the œsophageal wall by a short narrow pedicle around the base of which malignant infiltration of the wall can be seen. This pedunculated variety of œsophageal carcinoma, although well recognized, is distinctly rare. (*Fig.* 559.)

Histology.—Examination of sections from the operation specimen confirm the diagnosis by biopsy of squamous-celled carcinoma. There are, however, one or two additional features of interest.

Firstly, the degree of differentiation in the tumour varies greatly, not merely from one block of tissue to the next but even in different parts of the same histological section, well-differentiated and anaplastic components of the carcinoma being seen side by side in the same microscopical field. The differentiated areas form circumscribed islands, some of which show keratinization at their centres. The anaplastic cells are distributed singly or in small clumps in the fibrovascular stroma, thus giving the latter a 'sarcomatous' appearance. This combination of well-differentiated and poorly differentiated elements produces a histological pattern which suggests a mixed epithelial and mesenchymal tumour—a 'carcinosarcoma'. This suggestion is maintained in sections stained by Van Giesen's method and in those impregnated for reticulin. The reticulin outlines the well-differentiated groups within which there are very few argyrophil fibrils. By contrast the stroma containing the anaplastic cells shows a close meshwork of reticulin as seen in many cases of sarcoma. Nevertheless, careful examination reveals the identity and continuity of the

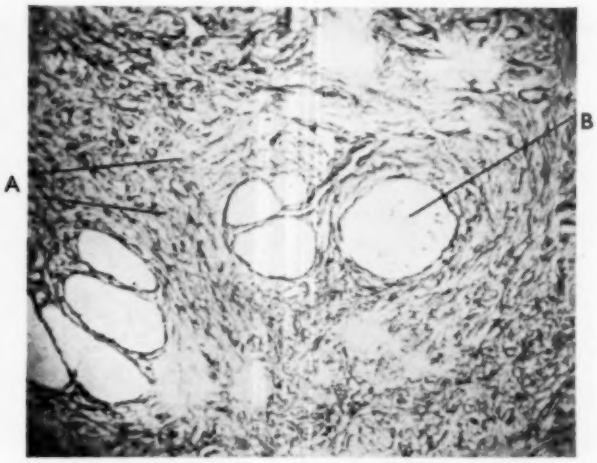

FIG. 562.—Microscopical appearance of the tumour. High power. (Reticulin impregnation.) A, Anaplastic carcinoma lying in a network of argyrophil fibres; B, Epithelial groups of well-differentiated carcinoma sharply outlined by reticulin.

tumour elements in the two types of tissue, for several sections show clear transition between the epithelial 'islands' and the anaplastic 'stroma'. At the periphery of the differentiated groups the cells can be seen to become spindle-shaped, to break away from the main mass and pass in amongst the fibroblasts and vessels of the supporting tissue. There would thus seem to be no doubt regarding the true histological interpretation. (*Figs.* 560-562.)

A second point of interest is the remarkable absence of necrosis even at the very tip of the pedunculated tumour despite the very narrow stalk.

Sections through the œsophagus at the base of the pedicle show invasion of the wall and surrounding connective tissue.

In view of the pathological report, the length of survival must be considered unusual.

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ANOMALOUS PERITONEAL ENCAPSULATION OF THE SMALL INTESTINE

A REPORT OF THREE CASES

By P. H. T. THORLAKSON

ASSOCIATE PROFESSOR OF SURGERY, UNIVERSITY OF MANITOBA; SURGEON, WINNIPEG GENERAL HOSPITAL; DEPARTMENT OF SURGERY, WINNIPEG CLINIC

I. W. MONIE

ASSOCIATE PROFESSOR OF ANATOMY, UNIVERSITY OF MANITOBA

AND T. K. THORLAKSON

TEACHING FELLOW IN ANATOMY, UNIVERSITY OF MANITOBA

To the surgeon, congenital abnormalities of the blood-supply of abdominal viscera and variations in the position and structure of these organs are of considerable importance. This is so because such error in diagnosis and be capable of complicating operative procedures.

The following three cases illustrate an unusual type of anomaly in which the small intestine lies

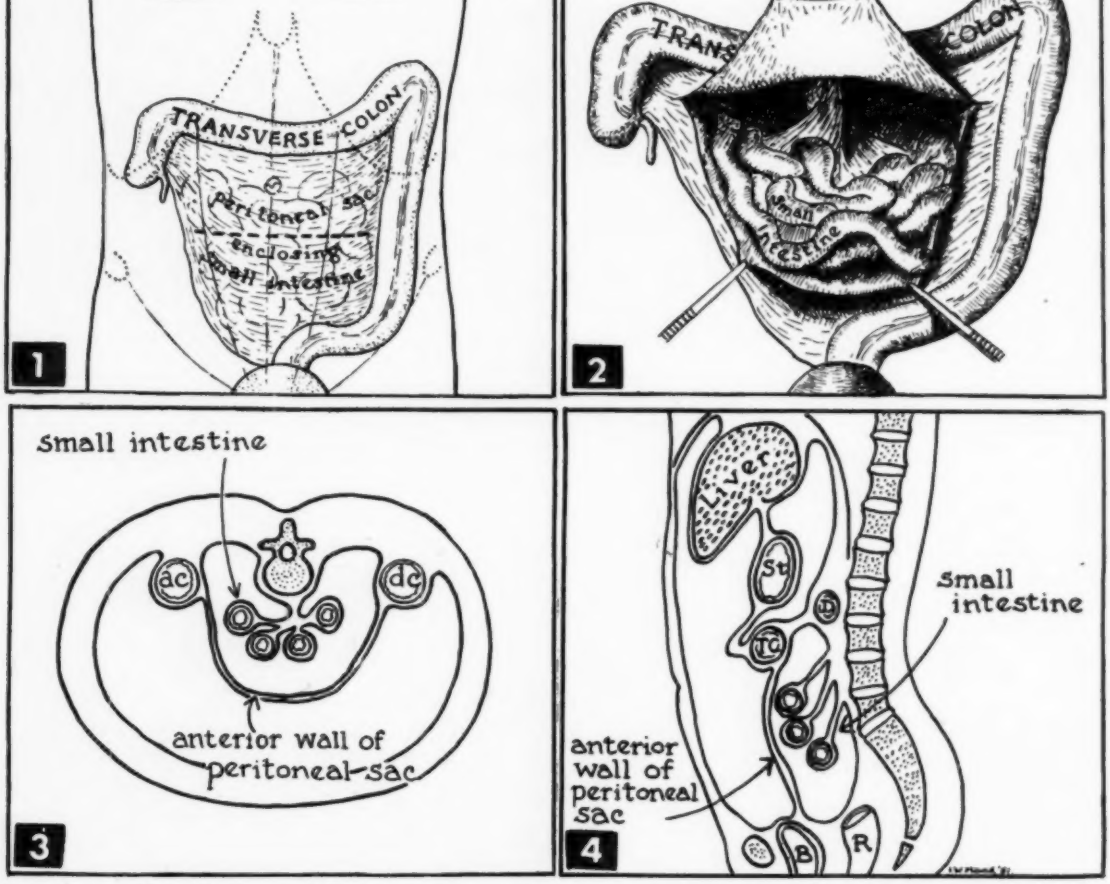

FIG. 563.—1, Shows the extent of the abnormal peritoneal membrane found in the three cases. 'High cæcum' was present in *Case* 3. The broken line indicates the line of the incision made in the sac wall. 2, The membrane has been incised and the sac contents displayed. Volvulus was present in *Case* 3. 3, Diagrammatic cross-section of the abdominal region showing the lateral attachments of the sac wall in both cases (ac, ascending colon; dc, descending colon). 4, Sagittal section of abdominal cavity showing vertical attachments of the sac wall (St, stomach; D, duodenum; T, transverse colon; B, bladder; R, rectum).

divergencies may be responsible for partial or complete bowel obstruction as a result of pressure, torsion, or occlusion. Furthermore, under certain circumstances, these anomalies may cause delay or posterior to an accessory peritoneal membrane. Apart from the presence of high cæcum and partial volvulus in one case, the relative positions of the viscera were normal.

CASE REPORTS

Case 1.—J. A., male, aged 64, first reported for examination in May, 1935, complaining of epigastric discomfort, anorexia, and constipation, all of about two years' duration. Epigastric discomfort was increased by the taking of food, and seemed to pass into the right upper quadrant; it was absent when the bowels moved daily. The patient had been on an ulcer régime; tarry stools had been noted on occasions.

PHYSICAL EXAMINATION.—Patient looked pale and undernourished. Apart from slight tenderness in the right upper quadrant, abdominal examination was negative; rectal and sigmoidoscopic examinations were also negative. No abnormalities were detected in other systems.

SPECIAL TESTS.—Examination of blood, urine, and stomach contents gave normal results. Stool specimens gave positive test for occult blood. The gall-bladder concentrated radio-opaque dye poorly, but no calculi were seen. X-ray examination of the gastro-intestinal tract was negative.

PROVISIONAL DIAGNOSIS.—Chronic cholecystitis and/or peptic ulceration. Because of his age, appearance, and indefinite history, the possibility of a gastro-intestinal malignancy could not be excluded and for that reason exploratory laparotomy was advised.

OPERATIVE FINDINGS.—Examination showed the small bowel lying posterior to an accessory peritoneal membrane (*Fig.* 563, **1**). This membrane was incised transversely and the small bowel exposed (*Fig.* 563, **2**); the peritoneal flaps were then excised. The membrane extended from the ascending to the descending colon (*Fig.* 563, **3**) and from the transverse colon to the pelvic viscera (*Fig.* 563, **4**). There was no opening in the sac wall other than at the points of entrance and exit of the small bowel, which seemed in no way affected by its unusual position. Gall-bladder, stomach, duodenum, and colon were found to be normal. Recovery was uneventful and although the patient's symptoms persisted after operation they did not incapacitate him. He returned for re-examination in March, 1951 (sixteen years later), and presented the same group of symptoms as in 1935. Re-investigation of his gastro-intestinal tract again failed to reveal an organic lesion.

Case 2.—E. B., male, aged 53, was admitted to the Winnipeg General Hospital on July 22, 1946, suffering from mild shock, forty-eight hours after being involved in an automobile accident. Examination revealed marked bruising of chest wall with possible rib fracture. The abdomen was distended, firm, and tender; otherwise physical examination was negative.

SPECIAL TESTS.—Blood-count—hæmoglobin 65 per cent; R.B.C. 3,320,000; W.B.C. 21,000. Urinalysis was negative. Radiographs of chest and abdomen were not contributory.

PROVISIONAL DIAGNOSIS.—Intraperitoneal hæmorrhage due to laceration of liver. Preparatory to operation a blood transfusion was given.

OPERATIVE FINDINGS.—The abdomen was opened through an upper right rectus incision. A large amount of dark free blood was encountered in the peritoneal cavity, but despite aspiration no viscera became visible. Stretched across the upper abdomen was a thick fatty membrane which lay anterior to the liver, gall-bladder, and stomach, preventing thorough examination of these structures; the transverse colon lay at its lowermost limit. This fatty structure was considered to be the greater omentum turned upward, with its free edge adherent to the liver, an attachment apparently not due to recent inflammatory reaction or adhesions. The right lobe of the liver and the gall-bladder were exposed by dissecting away the right margin of this structure, but no injury was discovered.

Attention was directed to a large cystic swelling in the lower part of the abdominal cavity which could not be fully examined through the original incision; accordingly, a lower incision was made on the left side. It was then observed that the small bowel lay entirely posterior to a thick peritoneal membrane, the lateral attachments of which could not be accurately determined at this stage. On incising this membrane, another collection of dark blood was encountered within the sac-like compartment behind it. The 'sac' was then opened completely and a considerable portion of its anterior wall removed. At this point it was determined that the lateral margins of the membrane fused with the peritoneum of the ascending and descending colons. Thus exposed, the small bowel was found to be normal and lying within a compartment of the general peritoneal cavity. No active bleeding was found from any structure in the lower abdomen. As it was now observed that blood entered the lower abdomen through an opening in the vicinity of the splenic flexure of the colon, search for the source of bleeding was renewed in the upper abdomen. The spleen was not injured. Further dissection of the 'omental' membrane revealed a deep and extensive anteroposterior laceration in the under-surface of the left lobe of the liver. Two rolls of oxidized gauze were placed in the depth of the laceration, as well as two Penrose drains, which were brought out through separate 'stab' wounds; the abdomen was then closed.

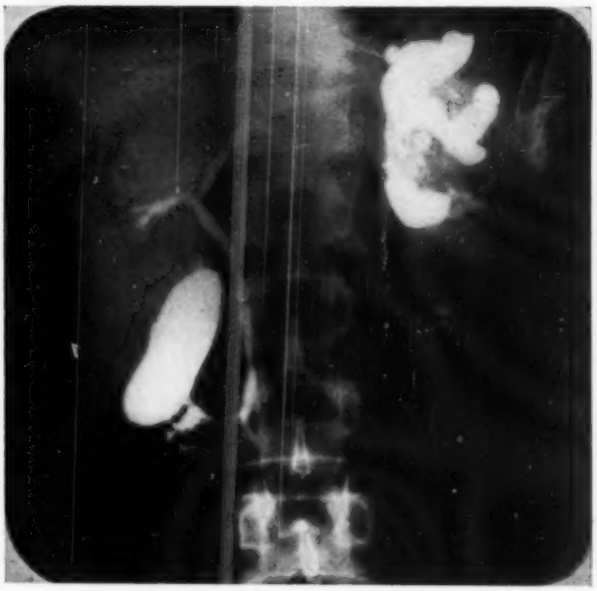

FIG. 564.—Injection of radio-opaque material into left lobe biliary fistula with visualization of common bile-duct and gall-bladder.

The depth and severity of the liver injury was later made manifest by the persistence of a biliary fistula, and injection of radio-opaque oil into this tract outlined the entire intrahepatic and extrahepatic biliary system (*Fig.* 564). The fistula ultimately closed spontaneously. The patient was discharged from hospital on Aug. 27, thirty-three days after operation.

Fourteen months later this man required gastric resection for a chronic posterior penetrating duodenal ulcer complicated by marked obstruction; dense adhesions between the upper end of the stomach and left lobe of the liver were then encountered.

Case 3.—H. B., male, aged 57, first reported for examination in December, 1948, complaining of attacks of diarrhœa with abdominal cramps for several years. Prior to the onset of this trouble, he had increasing constipation of the hyper-inspissation type. These

episodes of diarrhœa lasted one to two weeks, during which the bowels moved six to eight times in twenty-four hours. There was no evidence of blood, pus, or mucus in the stools, nor were they steatorrhœic. The attacks were separated by intervals of two to three days, during which there were no bowel movements, only gas being passed per rectum. Family, personal, and past histories were non-contributory.

PHYSICAL EXAMINATION.—Patient was well nourished. Abdominal, rectal, and sigmoidoscopic examinations were negative. Apart from mild hypertension, no abnormalities were detected in other systems.

SPECIAL TESTS.—Examination of blood and urine was negative. Gastric contents contained no free hydrochloric acid after histamine stimulation. Apart from a hypertonic colon and high position of the cæcum, X-ray examination of the gastro-intestinal tract was negative.

PROVISIONAL DIAGNOSIS.—Irritable colon with recurrent diarrhœa associated with achlorhydria.

The patient was placed on medical treatment consisting of a smooth, low-residue diet, antispasmodics, and glutamic acid. He improved on this treatment.

Patient returned to the Clinic in March, 1950. History at this time revealed that in December, 1949, he had suffered an attack of severe biliary colic. This was characterized by pain in the right upper quadrant and associated with nausea and vomiting but without jaundice. Since this attack he had felt an almost constant dull ache in the upper abdomen with post-prandial distress. Present examination revealed tenderness in the right upper quadrant; the gall-bladder was unable to be seen on two occasions. A diagnosis of cholelithiasis was made and operation advised.

Through an upper right rectus incision, the gall-bladder was removed and the common bile-duct explored. Further examination of the abdominal cavity was prevented by the presence of dense adhesions. Examination of the gall-bladder by a pathologist showed chronic cholecystitis with calculi. Recovery was uneventful.

One year later the patient suffered two attacks of severe midabdominal pain associated with vomiting. Physical examination revealed a large, tense mass extending from the left upper quadrant to the symphysis pubis and across the midline. The mass could not be felt per rectum. Intravenous pyelography, a barium series, and barium enema were negative. Clinical impression was that this mass was retroperitoneal in origin and probably represented a pancreatic cyst or a lymphoblastoma.

At operation a left paramedian incision was made through the abdominal wall down to a dense membrane which was adherent to the anterior parietal peritoneum. The first step of the operation consisted of separating the 'cyst wall' from the parietes. The appearance of the membrane at this stage suggested a pancreatic cyst. On incising the membrane a small amount of straw-coloured fluid escaped. Within the sac was a lobulated mass, the surface of which was white and œdematous. On closer inspection these 'lobules' were found to be loops of small bowel which had undergone partial torsion. On further exploration the membrane was found to cross the abdomen and to encapsulate the entire small bowel. The torsion involved 85 cm. of jejunum, in the centre of which was a constriction with considerable tumefaction of bowel above and below this point. After inspecting the entire length of small bowel, a resection of the involved segment was performed with end-to-end anastomosis. The abnormal membrane was widely excised. Where the small bowel entered the sac just below the duodeno-jejunal juncture, the edge of the sac was markedly thickened and arched over the root of the mesentery. This produced some degree of compression of the structures passing into the sac. This apparent compression was undoubtedly caused by swelling and thickening of bowel and mesentery because of the partial volvulus. Before closing the abdomen the lateral aspect of the membrane was found to fuse with the peritoneum of the ascending, descending, and pelvic colons.

In the resected segment of bowel, the pathologist described chronic inflammatory reaction with areas of marked subserosal fibrosis and acute serosal exudate.

POST-OPERATIVE DIAGNOSIS.—(1) Recurrent small bowel obstruction due to partial volvulus and adhesions. (2) Anomalous peritoneal reflection.

Recovery was uneventful and the patient was discharged on the thirteenth post-operative day.

EMBRYOLOGICAL CONSIDERATIONS

The accessory peritoneal membrane found in the three cases may be explained by abnormal return of the midgut loop to the abdominal cavity in the early stages of development.

The normal mechanism of midgut-loop rotation is illustrated in *Fig.* 565 (1–3). Shortly after its herniation into the umbilical cord during the sixth week of fœtal life, the midgut loop consists of a proximal (cranial) limb and a distal (caudal) limb, the junction of the two being at the point of attachment of the vitello-intestinal duct. About the tenth week of fœtal life the proximal limb returns to the abdominal cavity, pushing the mesentery of the hindgut over to the left (*Fig.* 565, 1); later, the distal limb returns and passes cranially to lie just caudal to the liver (*Fig.* 565, 2). As the liver reduces relatively in size, the supracæcal portion of the distal limb lengthens, allowing the cæcum to remain in the right iliac fossa. Ultimately, the mesentery fuses with the peritoneum of the posterior abdominal wall, excepting those portions of it which persist as the mesenteries of the small intestine, the pelvic colon, and the transverse colon (*Fig.* 565, 3). The proximal limb forms all the small intestine with the exception of its terminal portion; the distal limb gives rise to the terminal part of the ileum, the cæcum, the ascending colon, and approximately the right two-thirds of the transverse colon.

Variation in the normal mechanism is offered as an explanation for the presence of the abnormal peritoneal membrane found in the cases described. If, instead of the proximal limb, the distal limb returns first, the latter will come to lie in the region normally occupied by the derivatives of the former; namely, the sinistro-caudal portion of the abdominal cavity where it lies parallel to the hindgut (*Fig.* 565, 4); later, when the proximal limb returns, it will occupy a position to the right of the distal limb. If the distal limb now migrates cranially in an attempt to pursue its normal course of development, the dorsal mesentery attached to it will be carried ventral to the portion of small intestine which is derived from the proximal limb (*Fig.* 565, 5). In this way, most of the small intestine will be covered by that part of the original dorsal mesentery which ordinarily forms the transverse mesocolon. Fusion of portions of the dorsal mesentery and of the peritoneum of the dorsal aspect of the ascending colon, with the peritoneum of the posterior abdominal wall, then follows. While the transverse colon, by this process, is deprived of its mesocolon, another can be provided by adherence of the colon to the dorsal aspect of the greater omentum, an attachment which ordinarily takes place in any case. In this way the bulk of the small intestine will come to lie

behind a peritoneal membrane and thus be excluded from the greater peritoneal sac (*Fig.* 565, **6**). The attachment of the membrane to the descending colon and pelvic viscera and, in *Case* 2, the attachment of the greater omentum to the liver, may be accounted for by its adherence later to these structures.

COMMENTS

Three cases are reported representing an unusual developmental anomaly within the abdomen. In these three cases the small intestine lay free and normal behind a translucent membrane. The second case presented features similar to the first,

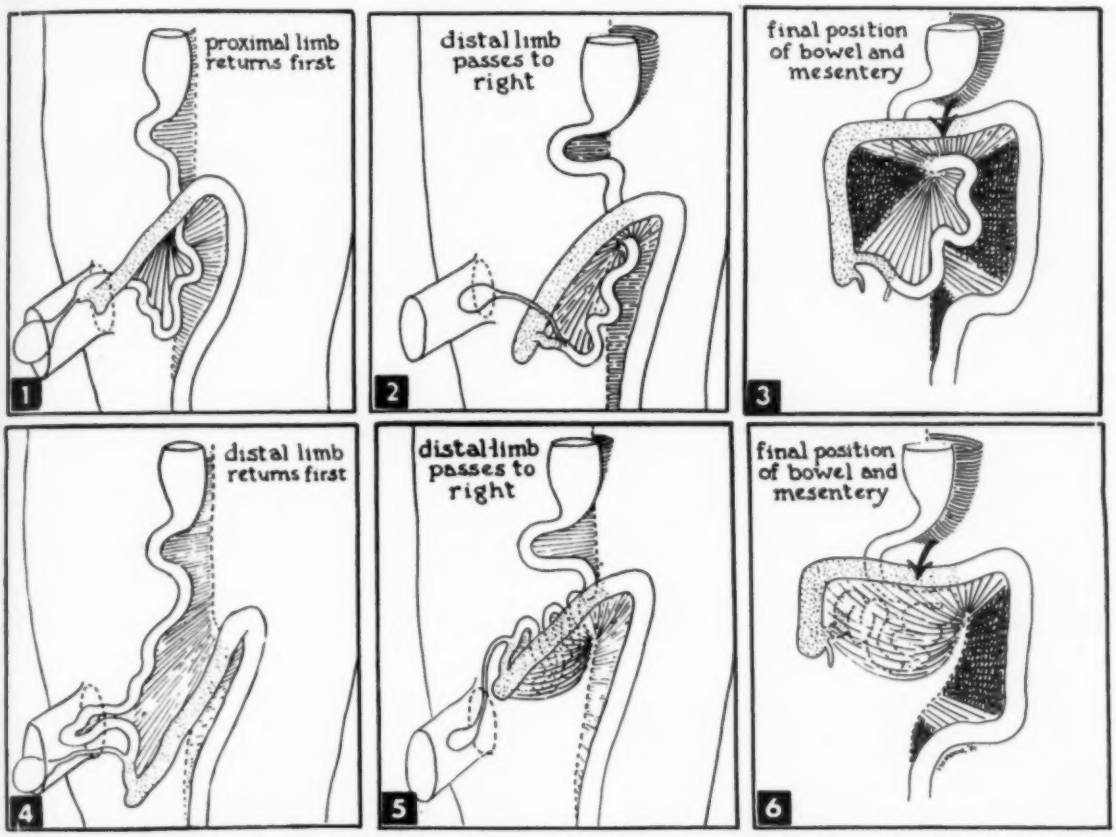

FIG. 565.—**1–3**, Normal development of midgut. **4–6**, Abnormal development of midgut which would explain the findings in the cases described. In (**3**) and (**6**) the arrows indicate the direction of growth of the greater omentum; the darkly shaded areas show the portions of the dorsal mesentery which fuse with the peritoneum of the posterior abdominal wall. The stippled portion of the gut indicates the distal limb of the midgut loop.

In *Case* 2 it was observed that there was an opening into the sac in the region of the splenic flexure of the colon. This opening might be accounted for by the incomplete attachment of the transverse colon to the posterior surface of the greater omentum in this region.

In *Case* 3 the presence of 'high cæcum' and short attachment of the small-bowel mesentery to the posterior abdominal wall are findings in favour of abnormal development.

Two cases with features resembling those described above have been found in the literature. Cleland (1868) recorded a case in which the small intestine was enclosed within a peritoneal sac, but, in this, the main ventral portion of the sac wall lay between the transverse colon and the stomach and there was an opening in the sac wall close to the ileocæcal junction. The case described by Lickley and Cameron (1907) closely resembles those described in the present report, although here the third and fourth parts of the duodenum were incorporated in the ventral wall of the sac, the superior mesenteric artery passing behind them.

but, in addition, the free border of the greater omentum had fused with the peritoneum of the edge of the liver. In the third case the membrane was greatly thickened and adherent to the anterior abdominal wall; a segment of jejunum had undergone partial volvulus, giving rise to subacute obstruction with marked inflammatory change in the intestinal wall and mesentery.

In each of our cases the congenital anomaly, *per se*, produced no symptoms and no characteristic radiographic findings. It was discovered at operation performed for an unrelated condition.

The authors are indebted to Professor Daniel Nicholson, Department of Pathology, Winnipeg General Hospital, and Professor Ian Maclaren Thompson, Department of Anatomy, University of Manitoba, for helpful advice and criticism.

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RETROPERITONEAL SARCOMA
WITH A REPORT OF FOUR CASES

By J. W. P. GUMMER
SENIOR SURGICAL REGISTRAR, CENTRAL MIDDLESEX HOSPITAL, LONDON

INCIDENCE

Recent surgical text-books make little reference to retroperitoneal tumours, and in particular to retroperitoneal sarcomata. Despite this lack of recognition, retroperitoneal sarcoma is a definite entity. In a recent review of 150 fibrosarcomata of all soft tissues, Cade (1951) reports 8 cases of retroperitoneal fibrosarcoma. McNamara, Smith, and Boswell (1940) also report 8 cases of retroperitoneal sarcoma. Donelly (1946), in a review of 95 retroperitoneal tumours, reports 18 cases of fibrosarcoma, and points out that such tumours occur sufficiently frequently to be considered in the differential diagnosis of any obscure abdominal mass ; a fact which is not generally appreciated. Donelly (1946) also comments on the interest which these tumours should have for general surgeons, urologists, and gynæcologists, which will be borne out by a perusal of the case-histories shortly to be presented. Slagerman (1937) reported on 144 cases of retroperitoneal sarcoma.

In the past three years, 4 cases of retroperitoneal sarcoma were admitted to the Central Middlesex Hospital, which is a general hospital of 850 beds. The diagnosis in all these cases has been proved by operation or by post-mortem examination. Three of the 4 cases were typical fibrosarcomata and occurred in male patients, and the fourth was a rather more obscure and anaplastic variety occurring in a woman.

PATHOLOGY

Retroperitoneal sarcomata arise independently in the retroperitoneal space and have no connexion with adult structures except by areolar tissue. They occur most often in the upper abdomen in close proximity to the kidneys, hence their interest to the urologist, but the perirenal sarcoma such as that recorded by Hanley (1948) is an unusual neoplasm.

The exact tissues from which retroperitoneal sarcomata arise is not known for certain. The origin of the perirenal sarcoma appears to be from the renal capsule and Handfield-Jones (1924) has postulated a possible origin from remnants of the embryonic urogenital system. Nichols (1947) has enlarged on this hypothesis.

Initially retroperitoneal fibrosarcoma appears to be an encapsulated, non-malignant neoplasm. Faith in the capsule of the neoplasm is often misplaced, for simple enucleation of a fibrosarcoma is all too commonly followed by a recurrence. The rate of growth is slow, but, after a varying period of time, often a matter of years, the tumour loses its apparent encapsulation and invades vital abdominal structures, making its complete removal a matter of great difficulty, if not an impossibility. Distant metastasis is a late occurrence and is uncommon, though Donelly states that of 82 malignant retroperitoneal tumours of all types, 30 per cent metastasized. The commonest site for metastases is in the lungs. In one of our cases pulmonary metastases did occur, but only after the tumour had been known to be present for seven years.

Macroscopically, retroperitoneal fibrosarcoma presents a lobulated appearance and is firm in consistency, though areas of softening from necrosis and hæmorrhage may occur. On cutting across the growth it appears to be yellowish-white in colour and presents a characteristic whorled appearance not dissimilar from that of uterine fibroids. Retroperitoneal fibrosarcoma may reach a great size, in some cases presenting initially as an abdominal tumour.

Microscopically the tumour usually presents a well-differentiated appearance, though anaplastic forms are known. Typically, well-formed fibres arranged in interlaced bands are seen ; mitotic figures are not common. These tumours are composed of fibroblastic tissue, but they may not reach the stage of adult fibrous tissue formation. The usual microscopical appearance of these tumours is shown in *Figs.* 566–569. *Fig.* 570 demonstrates the more anaplastic type in which fibre formation is less marked and mitotic figures frequent.

There is, therefore, in many cases very little microscopical evidence of malignancy. That these tumours are, in fact, sarcomata, though of a low grade of malignancy, and not fibromata, is borne out by a study of their clinical course during which recurrence, invasion of vital structures, and, ultimately, distant metastases occur.

CLINICAL FEATURES

There is no constant feature of retroperitoneal sarcoma from the clinical standpoint. All 4 cases presented here had differing signs, the commonest of which was a palpable abdominal mass, but even this feature was not present in one of them. The early symptoms are certainly vague, such as general malaise, loss of weight, abdominal discomfort, and, in one of our cases, pyrexia of unknown origin. Sudden severe abdominal pain may occur as the result of hæmorrhage within the tumour, but by the time this takes place, a mass is usually present which can be palpated without difficulty.

The tumour is usually situated in the upper abdomen to one side of the midline. It may be possible to detect some degree of lobulation by means of careful palpation. Tenderness is not marked and the tumour itself is, of course, dull to percussion, though bands of resonance due to overlying bowel may be present. The mass often moves with respiration.

It should be possible by means of careful investigation to establish the diagnosis before exploration.

A definite pre-operative diagnosis was not, however, made in any of the cases reported here, probably owing to a lack of consideration of the possibility of retroperitoneal neoplasm. The two investigations most likely to be of assistance in establishing the diagnosis are barium meal examination and pyelography. The barium meal examination will often show the stomach displaced from behind by the tumour in a manner not dissimilar from that which may be seen in carcinoma of the pancreatic body, which was, in fact, the radiological diagnosis in *Cases* 2 and 3, the films of which are shown in

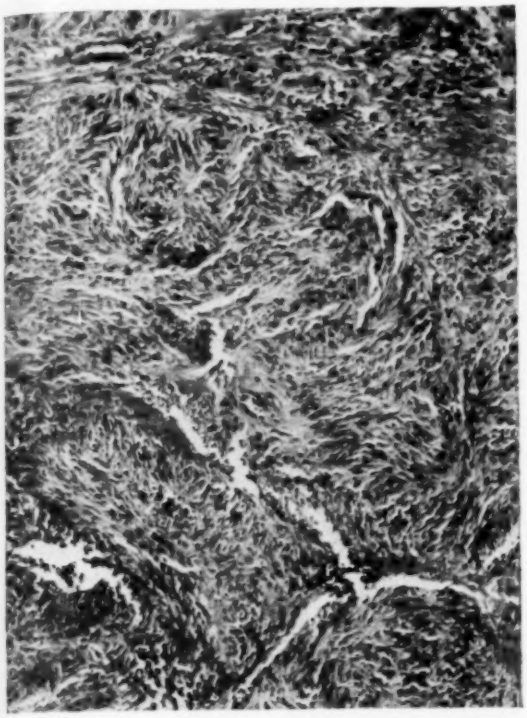

FIG. 566.—*Case* 2. Retroperitoneal fibrosarcoma. (× 78.)

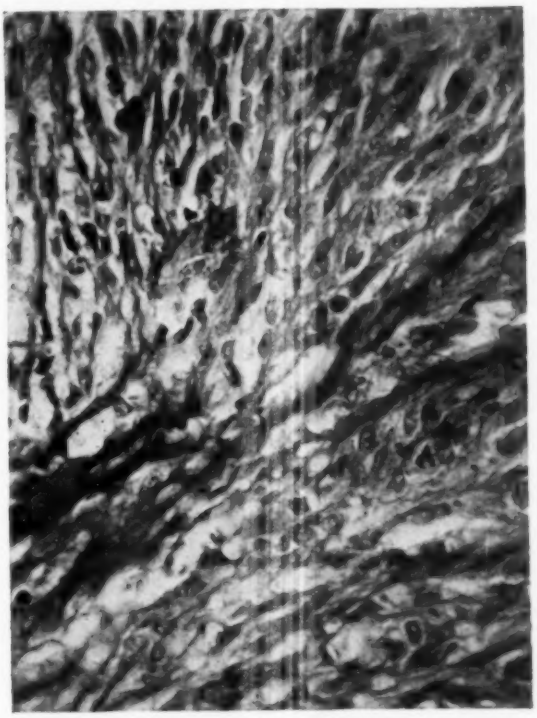

FIG. 567.—*Case* 2. Retroperitoneal fibrosarcoma. (× 330.)

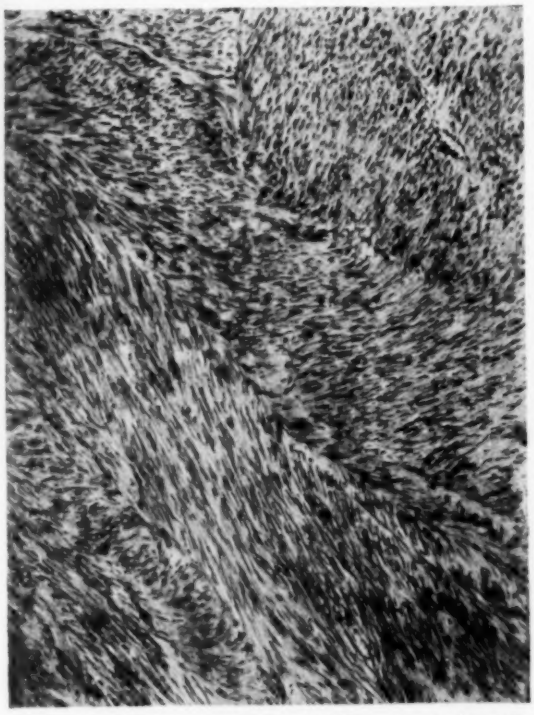

FIG. 568.—*Case* 3. Retroperitoneal fibrosarcoma. (× 78.)

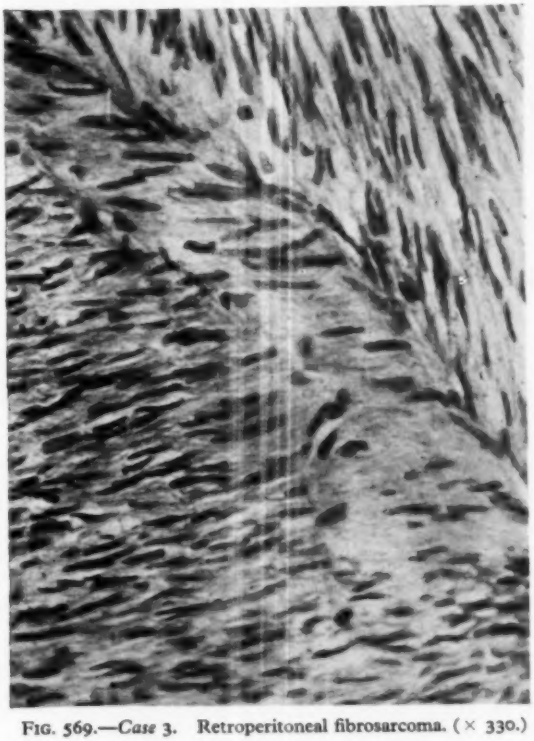

FIG. 569.—*Case* 3. Retroperitoneal fibrosarcoma. (× 330.)

Figs. 571–572. In this respect oblique or lateral views are of most help. Intravenous pyelography is only of value if the ureters are well shown. Renal distortion may be seen, but it is displacement of the ureter by the retroperitoneal mass which is a cardinal sign, and this is only well shown on retrograde pyelography.

Morton (1951) comments on the value of these two investigations when discussing the diagnosis of space-occupying lesions of the abdomen, and also

FIG. 570.—*Case* 4. Anaplastic retroperitoneal sarcoma, showing frequent mitotic figures. (× 78).

FIG. 571.—*Case* 2. Lateral view of barium meal examination showing forward displacement of the stomach.

FIG. 572.—*Case* 3. Anteroposterior and lateral views of barium meal, showing gastric displacement.

describes similar barium meal appearances in cases of carcinoma of the body of the pancreas and retroperitoneal tumours.

CASE REPORTS

Case 1.—A. H., a lorry driver aged 61 years, was admitted on Sept. 5, 1949.

On Admission.—He was lethargic and obviously a very ill man. Apart from his poor general condition it was difficult to find any definite complaint. His wife, however, stated that he was known to have had an abdominal tumour for seven years and that he had originally been diagnosed elsewhere as having a renal tumour. No operative treatment had been performed. At a further visit to the same hospital, pulmonary metastases had been diagnosed. Recently he had had some epileptiform seizures.

On Examination.—This revealed an emaciated man who was very weak. The abdomen was grossly distended and there were many enlarged superficial veins. The entire abdomen was occupied by a large craggy mass which was dull to percussion. The liver and spleen were not identified, and the kidneys were not palpable. Bowel sounds were not overactive and the rectum was empty. There were signs of bronchopneumonia in the chest. No abnormalities were detected in the central nervous system. A provisional diagnosis of abdominal carcinomatosis with pulmonary and possibly cerebral metastases was made.

A radiograph of the chest showed multiple rounded opacities in both lung fields with some degree of collapse in the right lower lobe (*Fig.* 573). The opacities were considered to be due to secondary malignant deposits. Plain radiographs of the abdomen showed apparent gross enlargement of both renal outlines. Multiple calcified

Fig. 573.—*Case* 1. Radiograph of chest showing multiple, rounded opacities due to metastatic deposits.

opacities were shown scattered about in both kidney areas, especially in the region of the lower pole of the left kidney (*Fig.* 574). The appearances suggested that the primary growth might be renal in origin, but it was impossible to say on which side, if it was so.

No further investigations were undertaken, for he was very obviously beyond surgical aid. His condition worsened and he died in coma on Oct. 25.

Post-mortem Examination.—A large, hard, irregular mass, 24 × 24 × 16 cm., was present, filling a large part of the abdomen. This was attached to the posterior wall of the bladder, but apart from distortion the bladder was otherwise normal and the ureters were quite patent. The growth was hard to cut, with areas of calcification. It was white in colour and showed numerous whorled areas resembling a mass of fibroids.

Stomach, intestines, liver, spleen, adrenals, and kidneys were all normal, and no intracranial metastases were demonstrated. Confluent bronchopneumonia with early abscess formation was present in both lower lobes, and scattered throughout both lungs were small hard nodules of secondary growth.

Histology.—A cellular growth which consisted of spindle-shaped cells, regular in shape, but varying in size. In some areas a loose reticular formation was present and in others there was necrosis. Mitoses were not numerous. *Conclusion*: Fibrosarcoma.

Comment.—This is an extremely interesting case, for it is a very good example of the natural history of the disease. In the first instance a relatively symptomless

Fig. 574.—*Case* 1. Plain radiograph of abdomen showing dense calcification, particularly in the region of the lower pole of the left kidney, but due to calcification in a retroperitoneal fibrosarcoma.

tumour was misdiagnosed as a more common condition. The error in diagnosis is easily understood, but it is less easy to appreciate why a diagnosis of renal tumour was made and no exploration carried out. It is, of course, possible that the patient may have refused operative treatment. It is evident from this case that retroperitoneal fibrosarcoma pursues a relatively benign course for many years, in this case probably for seven years, before taking on more malignant properties and metastasizing to distant organs. The areas of calcification demonstrated by X rays are not unusual in such long-standing tumours.

Case 2.—F. C. H., a watchmaker aged 60, was admitted on Dec. 9, 1950, to a medical ward. He was admitted for investigation into the cause of a fever of unknown origin and had been quite fit until a few days before his admission to hospital. It was thought possible that he was suffering from a virus pneumonia. The only point in the past history of any significance was that he had malaria during the 1914–18 war. There was an indefinite history of loss of weight.

ON EXAMINATION.—Clinical examination did not reveal anything definite, except a slight tenderness in the splenic region. X-ray examination of the chest showed no abnormality. Culture of the urine was sterile and there were no abnormal deposits. There was a persistent leucocytosis, averaging 18,000 W.B.C./c.mm. with 80 per cent neutrophils. The hæmoglobin was 61 per cent (Haldane). Repeated blood-cultures were sterile.

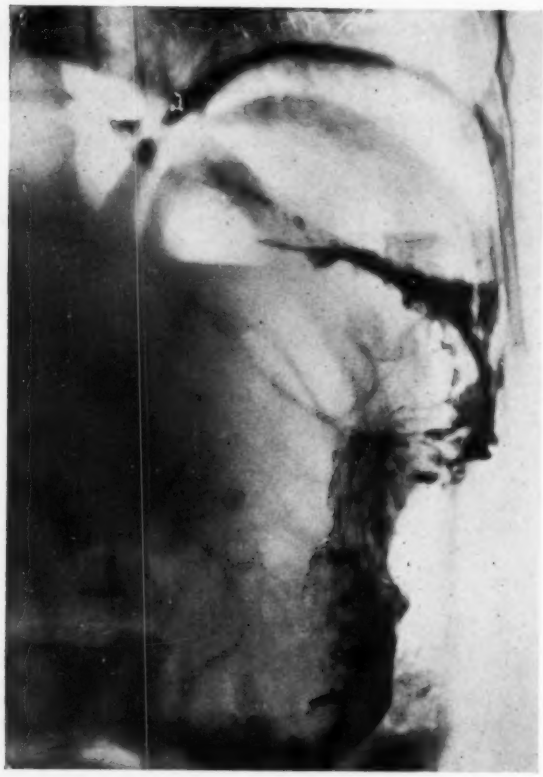

FIG. 575.—*Case* 2. Lateral view of barium meal, after induction of pneumoperitoneum. Indentation in posterior part of stomach.

Agglutination tests were all negative. In view of the persistent pain in the left flank the possibility of a left perinephric abscess was considered, but an intravenous pyelogram showed no abnormality. Barium meal and enema examinations were also normal. The pyrexia, leucocytosis, and slight tenderness in the splenic region persisted and the possibility of an underlying carcinoma of the pancreas was considered. A pneumoperitoneum was, therefore, induced, and a further barium series studied. This was reported on as follows: "A pneumoperitoneal barium meal showed a constant indentation of the posterior part of the stomach, which was accentuated with the patient in the supine position. Appearances are rather suggestive of a mass in the posterior left upper abdomen, possibly carcinoma of pancreas". (*Fig.* 575.) In view of this report, laparotomy was decided upon.

AT OPERATION.—A large lobulated, firm mass was found lying behind the stomach on the left side. The mass was attached to stomach, spleen, and pancreas. It was impossible to ascertain from what structure the mass arose. The mass was removed together with the tail of the pancreas, the spleen, and much of the posterior gastric wall. The posterior wall of the stomach was reconstructed and a drain led down to the site of pancreatic section. The wound was closed in layers.

The patient made a good recovery from the operation and was discharged from hospital three weeks later. He has since been seen in the out-patient department and is gaining weight. No mass is palpable.

PATHOLOGIST'S REPORT.—A malignant mass, 15 × 14 × 6 cm., posteriorly infiltrating the tail of the pancreas, the spleen, and the stomach. Microscopy shows a fairly well-differentiated fibrosarcoma. Mitotic figures occur, but are not conspicuous. *Conclusion*: Retroperitoneal fibrosarcoma.

Comment.—It would, of course, be possible to postulate that this was a primary fibrosarcoma arising from the stomach. The operative appearances were, however, against this, and the equal invasion of stomach, pancreas, and spleen suggest a neoplasm arising apart from these structures and invading them as it increased in size.

Case 3.—A maintenance engineer, aged 49, was admitted on May 3, 1951. He had been seen a few weeks before in the out-patient department, when he complained of a sudden sharp attack of upper abdominal pain and nausea which had by then passed off. His private doctor, to whom he had reported, noticed an abdominal tumour and referred him to hospital for advice. He was symptom-free when seen, but examination revealed the presence of a firm, not painful mass in the left upper abdomen which could be seen, as well as felt. The mass moved freely with respiration and transmitted the aortic pulsation. It was impossible to get above the tumour. In all other respects he appeared to be a fit patient. There were many possible diagnoses in this case, particularly as this man had spent much of his life abroad. Retroperitoneal tumour, pseudo-pancreatic cyst,

FIG. 576.—*Case* 3. Appearance of tumour after removal. (× ½.)

amœbic abscess, and liver hydatid were all considered. No amœbæ were found in the stools and the Casoni test was negative. A barium meal examination was carried out and this showed no abnormality within the stomach, but there was a definite forward displacement of the stomach as if by a retroperitoneal tumour (*Fig.* 572). It seemed possible to the radiologist that this might well be a carcinoma of the pancreas. Clinically this diagnosis appeared unlikely, as the mass moved much too freely with respiration.

AT OPERATION.—Exploratory laparotomy was carried out on May 11 through a left upper paramedian incision. A large retroperitoneal fibrous mass was found sitting astride the lesser curvature of the stomach. *Fig.* 576 shows the notch in the specimen which was occupied by the stomach. The mass was quite freely movable, and it was possible, with a little care, to remove the entire mass without causing damage to any vital structure. The wound was closed without drainage, and the patient made an uninterrupted recovery from the operation, being discharged from hospital on May 25.

PATHOLOGY.—A well-encapsulated fibroid. The cells were regular and spindle-shaped. The cellularity of the tumour was not constant. There were no nuclear irregularities and mitoses were not conspicuous. *Conclusion*: Fibrosarcoma.

Comment.—This may well be described as a typical retroperitoneal sarcoma. Apart from a short attack of pain probably due to hæmorrhage within the tumour, there were no symptoms, and a more or less chance occurrence brought to light an abdominal growth of some size.

Case 4.—E. G., a housewife aged 59, was admitted on May 26, 1948. She complained of abdominal pain and distension, and also constipation. She was sent to hospital by her practitioner as a case of subacute intestinal obstruction. She had always had a tendency to constipation, and for about two weeks prior to admission she had had some colicky abdominal pain. Two days before admission to hospital the pain had increased in severity and was referred mainly to the umbilical region. There was nothing of significance in the previous history.

ON EXAMINATION.—The abdomen was seen to be markedly distended and a large cystic swelling was felt, arising out of the pelvis to above the umbilicus. The mass was tense, and dull to percussion, and could be detected on pelvic examination. A diagnosis of ovarian cyst was made, and in view of the severity of the symptoms immediate laparotomy was advised.

AT OPERATION.—A soft, solid, necrotic tumour was found filling the abdomen and extending to halfway between the umbilicus and the costal margin. The mass was situated retroperitoneally and filled the broad ligament. The upper pole of the tumour was at the root of the mesentery and, in places, intestine was densely adherent to the tumour. An attempt was made to mobilize the tumour, during which there was some intestinal damage. The growth was manifestly inoperable, and after removing a fragment for biopsy the abdomen was closed.

BIOPSY REPORT.—"The material comes from an obviously malignant tumour which consists of round and spindle cells. There is no clear separation of tumour stroma and tumour parenchyma. There is widespread necrosis."

During the post-operative period she developed paralytic ileus and gross œdema of her left leg. She subsequently received a short course of X-ray therapy, but this was without avail, and she died on June 29.

POST-MORTEM EXAMINATION.—Huge spherical mass of tissue extending from the pelvis to the costal margin. Running across the upper pole was the transverse colon and its mesentery—these were free. Over its anterior surface were loops of small intestine and mesentery, firmly adherent. On its left side and adherent in the mass was the descending colon, bluish-black in colour, and its blood-supply had obviously been impaired. The tumour mass was friable, and a pale pink fleshy colour. At its lower pole the tumour mass appeared to involve the uterus. The tumour was retroperitoneal throughout. The liver and lungs were healthy and no metastases were detected elsewhere. Microscopy confirmed the previous biopsy report.

Comment.—This was a case of a more malignant tumour, the exact origin of which is obscure. The cells were much more immature and mitotic figures were numerous. It will be observed that both round and spindle cells were present in this neoplasm. Both Stout (1948) and Cade (1951) deplore the term 'spindle-celled sarcoma', and Cade groups all his cases of spindle-celled sarcomata with his fibrosarcomata. This type of tumour may be a different entity altogether, but it must be remembered that fibrosarcoma is a tumour of fibroblastic tissue and that the stage of adult fibrous tissue may not be reached.

TREATMENT

The treatment of choice in all cases of retroperitoneal sarcoma is surgical excision. The operation is most commonly carried out transperitoneally, though a lumbar approach may be used. It was pointed out earlier that these tumours in the early stages often have an apparent capsule, but enucleation is all too frequently followed by recurrence. However, when these tumours are relatively freely placed in the retroperitoneal tissues, as was *Case* 3, it is extremely difficult to know what other tissues and structures to remove in order that a recurrence may be prevented. Some authorities claim that a return of the tumour is not so much a recurrence as the growth of a small and separate neoplasm, missed at the first operation. It is well known that fibrosarcoma in other regions, such as the thigh, tends to recur after inadequate removal, but in this region a wide excision is usually a relatively simple matter.

A comparable excision of tissues in the retroperitoneal region is not possible, and if other structures have not been invaded, to remove adjacent important organs in the hope of preventing a recurrence would require great surgical courage, and would not be justifiable. Where vital organs have been invaded then extension of the surgical procedure is obviously essential if there is to be any hope of a cure, and *Case* 2 is an example.

By general consent radiotherapy is not of much value in the treatment of well-differentiated fibrosarcomata, though it may be of value in tumours such as that reported in Case 4. Cade (1951), in a review of some 153 fibrosarcomata arising from all sites, claims that his results have been helped by the judicious use of X-ray therapy. He points out, however, that a different technique is required for the irradiation treatment of sarcomata, as compared with that in common use for the treatment of carcinomata, entailing a lower total dose and especially a slower dose rate.

SUMMARY

1. The incidence of retroperitoneal sarcoma is discussed and 4 cases occurring in a general hospital in three years are described.

2. The importance of bearing the diagnosis in mind when dealing with any obscure abdominal tumour is stressed.

3. The vagueness of the symptoms and the aids to diagnosis are discussed. Barium meal after pneumoperitoneum may be of assistance.

4. The clinical histories of 4 cases, all with differing features, are presented.

5. Some points in the surgical treatment of retroperitoneal sarcoma are considered.

I wish to acknowledge the assistance that I have received in the preparation of this paper from all the members of the staff of the Central Middlesex Hospital, and in particular from Dr. Pagel and his assistants in the department of Morbid Histology, and from Dr. Pygott and his staff in the X-ray Department.

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CHRONIC INTUSSUSCEPTION DUE TO INVERSION OF A MECKEL'S DIVERTICULUM CONTAINING A CHRONIC PEPTIC ULCER, HETEROTOPIC TISSUES, AND A LIPOMA

BY R. E. GIBBINS
SURGEON, KIDDERMINSTER AND DISTRICT GENERAL HOSPITAL
AND W. ST. C. SYMMERS
SENIOR LECTURER IN PATHOLOGY, UNIVERSITY OF BIRMINGHAM

MECKEL'S diverticulum is not a common cause of intussusception. Harkins (1933) estimated that only about 1·5 per cent of all cases of intussusception are caused by Meckel's diverticulum. Intussusception, however, accounts for a considerable proportion of the complications of Meckel's diverticulum. The incidence of this complication is difficult to determine as the literature is confused and the data upon which some authors base their figures are vague. Thus, in an analysis of 201 published cases of complicated Meckel's diverticulum, Miller and Wallace (1933) mentioned 63 cases (31 per cent) of intussusception, while Harkins (1933) concluded from a more extensive study of the literature that 17 per cent of Meckel's diverticula which cause trouble do so by producing intussusception.

The following case is reported because it presented interesting clinical and pathological features.

CASE REPORT

HISTORY.—W. J., a housewife, born in 1919, began to have recurrent attacks of severe pain in the abdomen and right loin in September, 1947, three weeks after the birth at full term of her second child and a fortnight after the end of the lying-in period. Her first pregnancy, in 1945, had terminated in its twenty-sixth week; the child lived for only eight hours after birth.

The pain was felt deeply in the right side of the abdomen at the level of the umbilicus and in the right loin; it did not radiate. It occurred in attacks which varied in time of onset and duration. The attacks came on when she rose in the mornings or while she was up and about; they never occurred while she was lying down. Their duration ranged from about 20 minutes up to 2–3 hours; the shorter attacks were less severe. Between the attacks the patient was free from pain. The pain had no relation to meals, bowel action, or micturition. There was no generalized abdominal pain and she did not vomit. Her bowel habit was unaffected and there were no urinary symptoms. The attacks recurred intermittently for six months, after which she had no symptoms for more than two and a half years. Exactly similar attacks of pain, relieved only by antispasmodic drugs and pethidine, then commenced three weeks after her third pregnancy had terminated spontaneously in November, 1950, a month before full term, in delivery of twins, one of which was stillborn. The patient had left her bed a week after this confinement, and the first attack of pain came on two weeks later, shortly after she had had to hurry two miles home on foot to feed the baby.

On Jan. 10, 1951, five weeks after the attacks of pain had recommenced, the patient was admitted to a hospital elsewhere. She was well nourished, although not obese, and she looked healthy. Visible peristalsis was noticed when she was examined during an attack of pain. There were no other abnormal clinical findings. A barium meal and follow-through examination a few days after admission revealed no abnormality. A catheter specimen of urine contained no abnormal constituents and was sterile. Intravenous pyelography showed normal secretion by both kidneys; the right ureter was kinked in the vicinity of a calcified nodule, but it was not dilated and there was no evidence of hydronephrosis. The blood-urea was 29 mg. per 100 ml. A tentative diagnosis of intermittent obstruction of the right ureter was made. The patient was discharged from the hospital on Feb. 2, having had no further pain.

Four days later, on Feb. 6, she was admitted for the first time to the Kidderminster and District General Hospital under the care of one of us (R. E. G.), having had several further attacks of pain. No abnormality was found on clinical examination. Cystoscopy and right-sided retrograde pyelography were normal; the ureteric catheter was left in situ for 24 hours to 'splint' the ureter. She had no pain during the next five days and was again sent home.

FINAL ADMISSION TO HOSPITAL.—The patient was re-admitted to the Kidderminster and District General Hospital on March 1, 1951. Three days earlier she had had a severe attack of pain, during which her doctor had seen visible peristalsis. She had another attack two days after admission; no peristalsis was seen on this occasion and the only abnormal finding was slight resistance to palpation in the right hypochondrium; no mass was palpable. Rectal examination was normal.

OPERATION (R. E. G.).—On March 5, under thiopentone, nitrous oxide, oxygen, and ether anæsthesia, the abdomen was opened through an oblique right muscle-cutting incision at the level of the umbilicus, as it was thought that the right kidney and ureter were not above suspicion. An ileo-ileal intussusception was found about

12 in. (30 cm.) proximal to the ileocæcal valve. It was reduced fairly easily and was found to be due to a pedunculated 'polyp' within the lumen about 18 in. (45 cm.) from the valve. A length of ileum, including the 'polyp' and part of the intussuscipiens, which was very œdematous, was resected, and an end-to-end anastomosis performed. The calcific lesion which had been seen radiologically was found to lie in the right end of the transverse mesocolon and appeared to be a calcified lymph-node.

The patient made an uninterrupted recovery and was discharged home on the fourteenth day after the operation. Two years later, when she was last seen, she was in good health and had had no further symptoms.

THE SPECIMEN.—The specimen (*Fig.* 577) was examined in its fresh state. It was a 42-cm. length of the lower part of the ileum with its mesentery. The intussusception had been completely reduced.

The lumen of the intestine had been opened longitudinally near one end of the specimen by an incision midway between the mesenteric attachment and the antimesenteric border. This revealed a finger-shaped structure (*Fig.* 578), 5·5 cm. long by 1·3–1·7 cm. in diameter, which was attached at its base to the wall of the bowel on the antimesenteric aspect 11 cm. from the proximal end of the specimen. This structure was covered by apparently healthy, rugose mucosa, except at its tip, where there was a bulbous expansion which measured 2·1 × 1·5 × 1·3 cm. The greater part of the bulbous end was ulcerated and covered by a thin layer of brownish exudate; the ulcer had a smooth floor and a fairly sharply defined but shelving margin, the limits of which were obscured by the convexity of the surface.

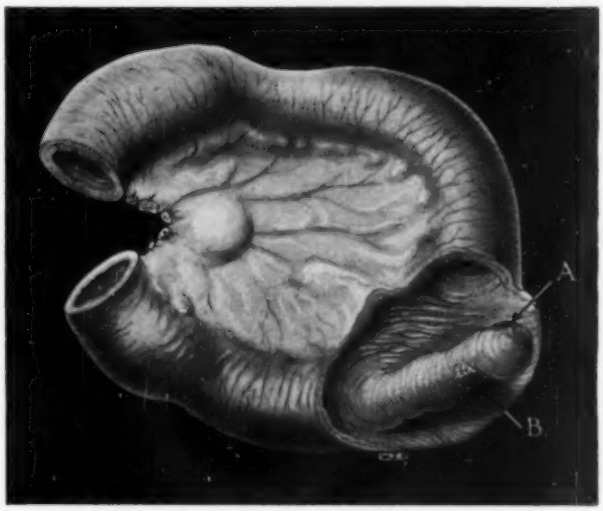

FIG. 577.—Resected ileum: partly opened, to show inverted diverticulum. A, Large ulcer at apex; B, Smaller ulcer. (× ½.)

FIG. 578.—Inverted diverticulum in situ, showing ulceration of its bulbous tip. (× 1·4.)

FIG. 579.—Inverted diverticulum in situ. The bulbous tip has been bisected, showing the deep peptic ulcer, hypertrophy of the muscularis, and the subserosal lipoma. (× 1·4.)

Just proximal to the bulbous end there was a second area of ulceration, 0·7 × 0·5 cm., in the floor of which the circular muscle coat was exposed; the outline of this smaller ulcer was sharp and its walls shelved steeply to the floor, which was at a uniform depth of about 0·2 cm. from the surface of the adjacent mucosa.

On the serosal surface of the specimen, at a site corresponding with the base of the polypoid protrusion in the lumen, there was a small, dimple-like depression. A tightly stretched, cord-like fold of fat-containing serosa arose in the form of a broad fan from the nearest point on the mesentery of the ileum and disappeared into the dimple; the fold contained a branch from the nearest of the distal arterial arches in the mesentery of the ileum. On exploring the floor of the dimple it was possible to pass a probe easily to a depth of 3 cm. within the polypoid structure, and with a small urethroscope it could be seen that the wall of this track was everywhere lined by normal serosa except at its blind end, where fresh fibrinous exudate gummed the surfaces together. It was thus apparent that the mass protruding into the ileum was an inverted diverticulum and that the taut fold of adipose serosa was its mesenteriole.

The bulbous expansion at the tip of the inverted diverticulum was bisected in its longest axis (*Fig.* 579), revealing a sharply circumscribed, soft, yellow mass, 1·2 cm. in its greatest dimension and situated between the tunica muscularis and the serosa at the apex of the diverticulum; the appearances were those of an encapsulated lipoma. On the bisected surface it was apparent that ulceration had destroyed the musculature of the tip of the diverticulum over an area 2·2 cm. in diameter; the limits of the breach in the musculature were sharp.

FIG. 580.—Mucosa of diverticulum, showing a coiled tubular gland of pyloric type (A) and crypts of Lieberkühn (B). (× 90.)

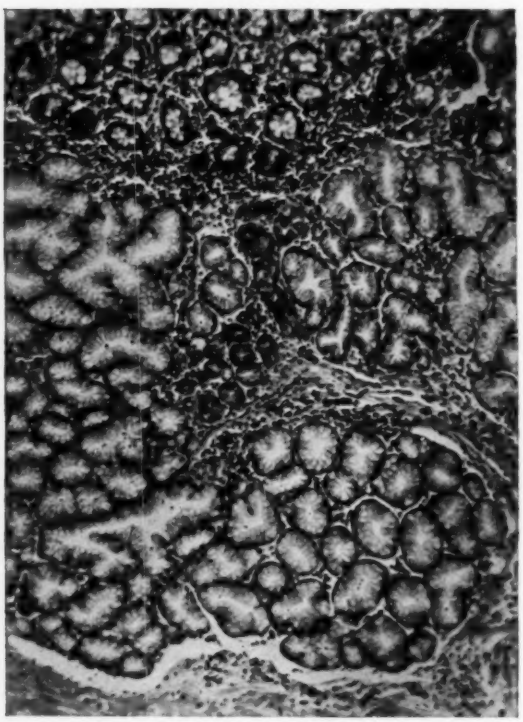

FIG. 581.—Mucosa of diverticulum, showing Brunner's glands. (× 90.)

The circular muscle coat was hypertrophied, measuring up to 0·3 cm. in thickness in the distal one-third of the sac. There was considerable fibrosis of the tissues adjacent to the ulcer, and much congestion and œdema beyond the zone of fibrosis.

HISTOLOGICAL EXAMINATION.—Two pieces of tissue were taken for microscopical study: (1) A slice including the whole area of the bisected surface of the bulbous apical mass; and (2) a wedge of tissue from the smaller ulcer. Both were fixed in formol-saline (4 per cent formaldehyde). Paraffin sections were stained by various methods.

1. *Apical Part of Diverticulum.*—There was a moderate amount of fibrosis of all coats of the wall of the diverticulum. The tunica muscularis, particularly its circular coat, was better developed than that of normal ileum, although fibrosis accounted for most of the thickening which had been noted macroscopically; the muscle cells were hypertrophied.

The large ulcer had the characteristics of an active, chronic peptic ulcer. A thin layer of fibrinous exudate and degenerating inflammatory cells covered a rather broader, necrotic zone of fibrinous and cellular exudate, with fibrinoid change in the connective tissue and vascular thrombosis. Beneath this zone there was vascular granulation tissue, separated by young, cellular cicatricial tissue from a broad zone of dense scarring. Over most of its extent the ulcer had breached and destroyed the tunica muscularis; the subserosa was thickened by fibrosis. Although there was much fibrosis in the margins of the ulcer, the muscle layers were here relatively little distorted and ended abruptly in the zone of necrosis.

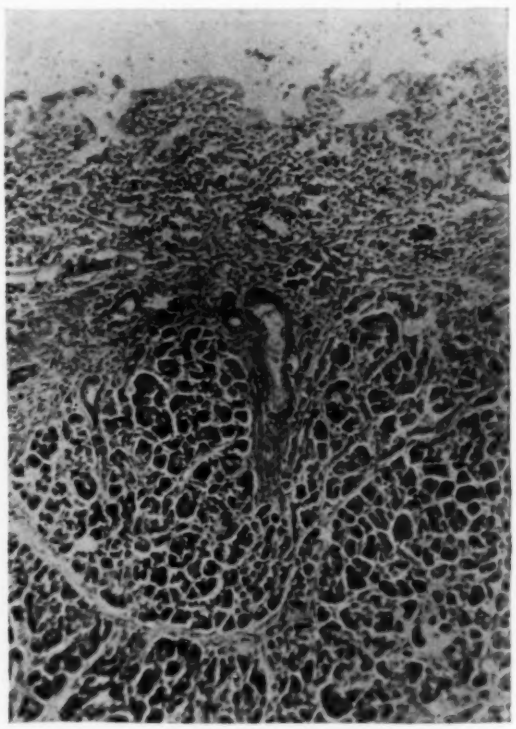

FIG. 582.—Pancreatic lobules in wall of diverticulum, showing ducts entering the overlying mucosa. (× 80.)

Endarteritis obliterans was much in evidence in the vicinity of the ulcer.

Most of the surviving mucosa was of small-bowel type and showed chronic catarrhal inflammatory changes, with moderate fibrosis of [illegible]na propria. There were scattered [illegible]oups of [illegible] alveoli situated

beneath the general level of the bases of the crypts of Lieberkühn. Serial sections showed that these were coiled tubular glands with the pattern and cytology typical of the pyloric glands of the stomach (*Fig.* 580). Some of them could be seen to be on the mucosal aspect of the muscularis mucosæ, but in most places there was such distortion of the latter by fibrosis of the mucosa and submucosa that its value as a topographical landmark was lost. Each of these glands opened into the bottom of a crypt of Lieberkühn through a narrow isthmus, in the wall of which there was an abrupt transition between pyloric-gland cells and Paneth cells.

Within a distance of 0·25 cm. from the edge of the ulcer there were a few small groups of gastric glands of fundic type, lined by chief and parietal cells; crypts of Lieberkühn were interspersed between these groups. About 0·8 cm. from the edge of the ulcer there was a group of typical Brunner's glands (*Fig.* 581), situated partly in the mucosa but mainly external to the plane of the muscularis mucosæ.

There was a circumscribed group of pancreatic lobules (*Fig.* 582) beneath the muscularis mucosæ, 1·5 cm. from the margin of the ulcer; mural fibrosis was minimal in this area. No islet tissue was seen. In the sections the longest dimension of the pancreatic nodule was 0·3 cm. Its ducts were of the interlobular type and opened into the adjacent mucosal glands.

The subserosal tumour at the apex of the diverticulum was a typical lipoma consisting of mature fat cells. It was surrounded by a distinct fibrous capsule, except where the inflammatory reaction beneath the floor of the ulcer involved its periphery; in this area there was some fat necrosis.

2. *Smaller Ulcer.*—The small ulcer was histologically similar to the large one described above. It had penetrated considerably less deeply into the muscular coat. The sclerosis in its margin had drawn the tunica muscularis and the muscularis mucosæ together. The adjacent mucosa was of ileal type.

DISCUSSION OF THE PATHOLOGICAL FINDINGS

The situation of the diverticulum on the antimesenteric aspect of the lower part of the ileum and the presence in it of heterotopic alimentary tissues are evidence that it was a Meckel's diverticulum. The unusual features of the diverticulum are: The variety of heterotopic tissues found; the co-existence of two complications, namely, peptic ulceration and inversion of the sac with ileo-ileal intussusception and the presence of a lipoma.

Heterotopic gastric, duodenal, and colonic mucosa and pancreatic tissue may occur in Meckel's diverticula, usually at the apex. Ducts of biliary type were described by Greenblatt, Pund, and Chaney (1936) in one of their cases of pancreatic heterotopia. Heterotopia has been variously stated to occur in 12 to 61 per cent of these diverticula; many of the published figures, however, give an unreliable impression of its incidence, as they are based on the findings in specimens resected because of complications. Material so obtained cannot be considered to be unselected, particularly as there is evidence that the two commonest heterotopias predispose to complications, namely, gastric mucosa to peptic ulceration and its consequences, and tumour-like masses of pancreatic tissue to invagination. Heterotopic gastric tissue is commonest, pancreatic tissue occurs considerably less often, and duodenal or colonic mucosa rarely. The presence of more than one type of heterotopic tissue is rare; co-existence of gastric and pancreatic tissue is least uncommon.

In the case reported in this paper the nature of the heterotopic pancreatic and duodenal tissue and of the gastric glands of fundic type was unmistakable. The glands of pyloric type, although possibly heterotopic, may have developed metaplastically in the mucosa of small-bowel type which lined the greater part of the diverticulum. Metaplasia of intestinal mucosa seems to be the most probable explanation of the comparable occurrence of glands of pyloric type occasionally observed in the mucosa in a variety of chronic diseases of the small intestine, as has recently been described by Liber (1951) in cases of Crohn's disease.

The presence of heterotopic gastric mucosa in a Meckel's diverticulum may lead to peptic ulceration. The ulcerative process usually develops in those parts of the diverticulum which are lined by the vulnerable intestinal mucosa. Ulceration of the adjacent ileum itself has been described (Maddock and Coventry, 1941). It is noteworthy that in our case chronic peptic ulcers developed in a diverticulum in which duodenal and pancreatic tissue was present; if the apparently normal structure of these glands was reflected in their production of normal secretion, it might have been expected that the alkalinity of the latter would have had some neutralizing effect on the secretion of the heterotopic fundic glands. As it was desired to preserve the specimen in as intact a state as possible, not enough tissue could be examined microscopically to determine whether more gastric mucosa was present than was found in the available sections, although the existence of active peptic ulceration makes this a reasonable assumption. No identifiable foci of heterotopia could be detected in the fresh specimen, even by examining it with the low-power binocular dissecting microscope; with the latter all of the non-ulcerated area of the diverticulum was seen to be covered by seemingly normal, villous mucosa of ileal pattern.

As with peptic ulcers elsewhere, hæmorrhage or perforation may complicate such ulceration of Meckel's diverticulum. In our case the hollow serosa-lined core of the inverted diverticulum was partly sealed by fibrinous exudate which ultimately would have led to its obliteration; it is tempting to speculate whether the inversion had thus resulted in an effective protection against intraperitoneal perforation of the ulcer, which had already extended so far through the muscular coats that in places its floor was separated from the serosa only by granulation and scar tissue.

In 26 of the 114 recorded cases of intussusception of Meckel's diverticulum which Harkins (1933) analysed, a 'tumour' was present at the tip of the diverticulum. Harkins also commented that intussusception complicated more than half of the 49 published cases of tumour of Meckel's diverticulum; his statement that almost one-third of these 'tumours' contained pancreatic tissue indicates that in a considerable number of the cases the lesion in question may have been purely a mass of heterotopic tissue and not a neoplasm.

True neoplasms of Meckel's diverticulum are very rare. Argentaffinoma has been reported, as well as unequivocal carcinomata and sarcomata.

Benign neoplasms which have been recorded include adenoma, papilloma, leiomyoma, and lipoma. In view of the presence of a lipoma in our case, it is of interest that Foster (1947) described a case in which inversion and intussusception of a Meckel's diverticulum was associated with a submucosal lipoma at the apex of the latter, and comparable cases are on record.

It is probable that intussusception complicating Meckel's diverticulum is initiated by inversion of the diverticulum. Harkins (1933) observed that in all but one of the published cases which he reviewed in which the apex of the intussusceptum was formed by a Meckel's diverticulum, the diverticulum itself was inverted. Simple inversion of Meckel's diverticulum without intussusception of the ileum is likewise very rare. With regard to the pathogenesis of the inversion of the diverticulum which we have described, the subserosal situation of the apical lipoma would seem to preclude the possibility that inversion resulted by a mechanism similar to that by which a polypoid mucosal growth may lead to invagination of the bowel wall. In the case of the latter it is not difficult to believe that the polypoid mass might be gripped by peristaltic contractions of the bowel and passed along the lumen, causing the wall at its site of attachment to be drawn inwards, with the eventual development of intussusception. It is, however, possible that the callous ulcer at the apex of the diverticulum in our case might have acted in this way, as a bolus-like mass leading to inversion of the sac. Such a mechanism is illustrated diagrammatically by Edwards (1939) in explanation of the development of intussusception as a complication of tumours of Meckel's diverticulum. We have found no previous record in the literature of the association of peptic ulceration in Meckel's diverticulum with intussusception.

COMMENT ON THE CLINICAL ASPECTS

Harkins (1933), in his review of 114 cases of intussusception of Meckel's diverticulum, listed a number of features which distinguish this type from ordinary intussusception. His conclusions were: Intussusception due to Meckel's diverticulum occurred in older patients (average age 13·1 years); a history of previous attacks was more frequent; the course of the disease was more chronic, and a mild attack often occurred a day or so before the major crisis; vomiting was severer; if a mass was palpable at all it was most frequently in the right half of the abdomen; rectal examination revealed a 'tumour' in a much smaller proportion of cases; bleeding per rectum was less profuse. It is noteworthy that in our case there was no vomiting at any time, no mass was palpable, rectal examination was normal, and there was no history of the passage of fresh or altered blood per rectum.

In their review of peptic ulceration as a consequence of Meckel's diverticulum, Aschner and Karelitz (1930) stated that the commonest symptoms of this complication were, in order of their frequency, the passage of fresh blood or clots per rectum, abdominal pain, which usually had no specific characteristics, and symptoms due to perforation and peritonitis. The only one of these symptoms present in our case was pain.

From the clinical standpoint our case presented several other interesting features:

1. Symptomatology.—

a. The Length of the History.—The attacks of pain began three years before the intussusception was recognized at operation in March, 1951. They recurred over a period of six months, after which there were no symptoms for two and a half years, until the return of the pain thirteen weeks before the operation. The patient was questioned in detail about her previous health, and nothing was elicited which in the least suggested earlier symptoms due to the diverticulum. She had never had dyspeptic symptoms or noticed blood in her stools, and there was no history of pain in the abdomen or back prior to the attacks which followed her second confinement, at the age of 28.

b. Pain.—The patient's only symptom was colicky pain, which was strictly localized in the right side of the abdomen and right loin. There was no generalized abdominal pain or vomiting, such as is typical of obstruction of the small intestine. The symptoms seemed at first to indicate a renal or ureteric lesion and led to the appropriate investigations.

c. Visible Peristalsis.—Visible peristalsis was not a constant feature of the attacks, although it was seen on two occasions, at an interval of seven weeks, during attacks which were described by the patient as particularly severe.

d. Findings on Palpation.—No tumour was felt, even on repeated examination during the attacks, but just before the operation definite resistance was found in the right hypochondrium.

2. Correlation of the Pathological Findings with the Symptomatology.—But for two factors, it would have seemed probable that the pain was due to the peptic ulceration and that intussusception was of very recent occurrence. The first of these factors was the patient's certainty that throughout the course of her illness the attacks of pain varied only in intensity and duration, never in situation or in other characteristics, and that the variations in intensity and duration had been noticeable since the beginning of the illness. Secondly, visible peristalsis, which was observed twice, eight weeks and one week before the operation, was a feature of attacks which differed from most other attacks only in their particular severity, although they were not the severest during which the patient was examined. It seems, therefore, to be possible that chronic intussusception, or at least inversion of the diverticulum, was present throughout the illness and that the attacks of pain were due to the resulting partial obstruction of the ileum. Nevertheless, it is not possible to exclude peptic ulceration as the cause of the pain *ab initio*, with inversion of the diverticulum and intussusception developing as a comparatively late complication, at about the time when visible peristalsis was first seen. The ease with which the intussusception was reduced at operation, the absence of adhesions, other than fresh fibrinous exudate in the tip of the serosa-lined core of the inverted diverticulum, and the absence of any apparent hypertrophy of the musculature of the ileum are observations which weigh against the possibility that inversion or intussusception was of long duration. There can,

however, be no doubt that visible peristalsis during the attack of pain eight weeks before the operation indicates that partial intestinal obstruction was then present. Our use of the epithet 'chronic' in relation to the intussusception in this case seems, therefore, to be justified.

3. **Relation to the Pregnancies.**—The patient's first pregnancy terminated 14 weeks prematurely; the puerperium was uneventful and there were no attacks of pain. Pain occurred for the first time three weeks after her second confinement. It reappeared after the third confinement, and again the interval between parturition and the onset of pain was three weeks. On both occasions she had lain in for a week after delivery. On the second occasion the attacks of pain commenced after unaccustomed exercise; there was no history of any unusual exertion preceding the pain at any other time.

It is possible that changes in intra-abdominal pressure and anatomical relations after delivery may in some way have precipitated the development of intussusception, although the mechanism by which this might have occurred is not obvious and the latent period of three weeks between delivery and the onset of symptoms cannot be explained readily, particularly as the patient had been up and about for two weeks before pain occurred.

SUMMARY

A case of chronic intussusception complicating inversion of a Meckel's diverticulum which contained two peptic ulcers is recorded. Recurring attacks of localized pain in the abdomen and loin at first suggested a high ureteric obstruction. Diagnosis was confused by the presence of a kink in the right ureter adjacent to a calcified nodule in the mesocolon. It is suggested that the pain may have been due either to inversion of the diverticulum and intussusception *ab initio* or to the peptic ulceration.

The patient was a young woman whose symptoms first appeared three weeks after parturition and recurred at the same interval after her next confinement.

Resection of part of the ileum with the diverticulum, after reduction of the intussusception, relieved the symptoms completely.

The diverticulum also contained a lipoma. In addition, gastric glands of fundic type, duodenal mucosa, and pancreatic tissue were present. Glands of pyloric type were also present and may have been heterotopic or of metaplastic origin.

We wish to thank Professor F. A. R. Stammers for his interest in the presentation of this case. We are indebted to Mr. W. J. Pardoe for the drawing of the specimen.

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PLASMA-CELL MASTITIS

BY GORDON F. CASSIE, WEST MIDDLESEX HOSPITAL

THE occurrence of a case of this rare but important surgical condition of the breast, and observation of all of its clinical stages, prompted a search of the British literature which revealed only one paper on the subject, by Cutler (1949), his cases having been drawn from America.

The term was first suggested by Ewing for the first 10 cases that were studied by Cutler and Adair (Adair 1933) in the United States. A description of the condition was included in the monograph on the breast by Cheatle and Cutler (1931), which was published in this country as well as in America; in it they emphasize the difficulty in microscopical diagnosis in some cases. Hoerz (1910) reported a case of mastitis due to trauma which he called 'mastitis obliterans', but this may have been fat necrosis. Schultz (1933) described 10 cases with clinical histories under the name of 'plasma-cell mastitis' and claimed that the condition could be diagnosed clinically; he asserted that it is precancerous. Rodman and Ingleby (1939) reported a case which showed marked shock and toxæmia following a radical breast amputation; they attributed this to fat-splitting enzymes acting upon colostrum-like substances and claimed that their animal experiments tended to support this view. Cromar and Dockerty (1941) found 24 specimens out of 12,000 cases operated on for benign and malignant breast conditions in the Mayo Clinic. They emphasized the points in differential diagnosis from tuberculosis under the microscope. Payne, Strauss, and Glasser (1943) declare that the term 'plasma-cell mastitis' is superfluous and that the plasma cells are not pathognomonic of anything; they prefer to continue the term 'mastitis obliterans'. Parsons, Henthorne, and Clark (1944) found 5 cases out of 1500 specimens in Mississippi, but the clinical history was available in only 2 cases. Gaston (1947) recorded a case in which a comedo carcinoma was found to have developed in the presence of a plasma-cell reaction; he quotes this case and the metastasizing plasmocytoma reported by C. W. Cutler (1934) as support for the belief that plasma-cell mastitis may become malignant.

Cutler (1949) made an excellent survey of the condition, and he records a unique case of the disease in both breasts and stresses the difficulties in

diagnosis, especially the difficulties which face the pathologist in a frozen section. Cromar (1949) refutes the idea that the condition might be diagnosed clinically and appeals for biopsy; he suggests that the term 'stale milk mastitis' would be more appropriate.

Aetiology.—There is general agreement that the condition is a periductal inflammatory reaction due to extravasation of duct contents. Cutler (1949) attributes the extravasation to intraductal degeneration of retained secretions, whilst Parsons and others (1944) postulate a focal infection of the duct wall. Cromar believes retention of milk products to be an adequate explanation and quotes the animal experiments of Rodman and Ingleby (1939) as support for this hypothesis. Cromar and Dockerty (1941) found a history of difficult nursing in over 50 per cent of their cases. Cole (1944) declares that fat necrosis may be the chief factor responsible for the reaction both in plasma-cell mastitis and fat necrosis of the breast. The following factors appear to be characteristic of the affection: (*a*) parity and lactation; (*b*) age approaching 40; (*c*) minor traumata—these are so common in a woman's life that they would not appear important to the patient. In the case to be recorded a definite history was elicited of trauma at the same site two weeks before its onset.

In order to link up these factors, it is suggested here that trauma is responsible for the damage to the ducts and consequent extravasation of fat droplets and fatty-acid crystals; these provoke a plasma-cell reaction in breast tissue which is under a waning progesterone influence.

Clinical Picture.—The condition appears in parous women at the age of 40, or approaching that age, who have breast-fed, and it passes through three phases:—

1. *Acute or Reactive Phase.*—The patient usually attends her family doctor complaining of a painful breast, which shows a large, reddened, hot, tender, indurated mass obviously involving breast substance and not merely the subcutaneous fat. More than one quadrant is usually involved. The overlying reddened skin is tethered to the mass, which is very firm and acutely tender. There may or may not be a history of trauma elicited. A creamy discharge sometimes occurs from the nipple, which may be retracted. The axillary glands may be enlarged, soft, and tender. This acute stage lasts for about two weeks, uninfluenced by the administration of penicillin or sulphonamides, and it resembles the early acute breast abscess seen in nursing mothers. It is possible that the clinical picture in the acute stage may be confused with traumatic fat necrosis.

2. *Subacute or Localizing Phase.*—This lasts for two to three weeks, during which time the reddened area becomes much reduced in size and the hard mass more discrete. This stage resembles a localizing abscess which has become of low grade owing to the bacteriostatic action of penicillin.

3. *Chronic or Resolving Phase.*—During the chronic phase the mass occupies a position deep in breast tissue, loses its tenderness, and daily regresses in size; meanwhile the overlying skin resumes its normal appearance, with the exception that it still puckers when pinched. The process of resolution may take up to three months or longer, but at the end of that time the breast has usually returned to its original state. Should the patient present herself for examination during this phase, the condition will undoubtedly and unhesitatingly be diagnosed as carcinoma, unless careful questioning has brought to light its previous course.

Macroscopical Appearance.—The involved breast tissue grates on cutting like a scirrhous carcinoma, and the cut surface has a similar pearly-white appearance but is interspersed with characteristic yellow flecks and patches; its limits are not sharply defined. Creamy debris may be expressed from the ducts.

Microscopical Appearance.—Microscopy shows periductal masses of infiltrating cells, most of which are characteristic plasma cells, the rest being leucocytes and macrophages. There may be occasional giant cells. The ducts are stuffed with similar cells and debris, and their epithelium may exhibit heaping (hence the name of mastitis obliterans). Occasional collections of fatty-acid crystals may be found embedded in fibrous tissue. The picture of giant cells and aggregations of other cells might at first sight suggest tuberculosis (hence the early term of 'pseudotuberculosis'); but in fact the distribution in that disease is perivascular and perilymphatic, not periductal as in plasma-cell mastitis. In contradistinction to traumatic fat necrosis there is an absence of fat granule cells.

CASE REPORT

Mrs. V. P., aged 40, attended the out-patient clinic of Mr. J. Scholefield on Nov. 9, 1950, having been referred by Dr. Scoones. She had had four children, the last birth four years previously; all the children were breast-fed and she had had no previous trouble with the breasts. She complained of a painful right nipple one month before and of a painful reddened lump in her right breast for two weeks, gradually increasing in size during that time. Her own doctor commenced penicillin therapy. She admitted to an accidental blow by an elbow on the same area of breast two weeks before the appearance of the mass.

Examination revealed the tender, reddened, hard mass, 4 by 3 in. (*Fig.* 583), involving breast tissue in the upper and lower medial quadrants. The skin was tethered to the mass; the nipple was at the same level as the left and not retracted. No axillary glands were palpable and the temperature was normal. The condition was assumed to be an acute mastitis and the penicillin was continued.

She was next seen five days later when the mass appeared to be more localized; she was referred to the casualty department for exploration as it was believed that there might be a small loculus of pus in the centre. A radial incision produced only a little blood, but a deep cut into the mass gave the very characteristic feel of a scirrhous carcinoma; indeed, a nurse at the opposite side of the theatre commented upon the grating noise made by the knife. A liberal biopsy of the tissue was taken and the wound sutured. A rapid paraffin section was made next morning and diagnosed as plasma-cell mastitis (*Figs.* 584, 585). The sutures were removed seven days later, when the mass measured 3 by 2½ in. (*Fig.* 583); ten days later the dimensions were 1½ by 1 in. and by Dec. 5, eight weeks from onset, only a little diffuse induration remained. Re-examination at two and six months after onset showed a normal breast.

DISCUSSION

The acute stage of plasma-cell mastitis will usually be diagnosed as a simple mastitis. The subacute stage resembles a breast abscess which has

become low grade owing to penicillin therapy and will probably be subjected to exploration; this is unfortunate, for a biopsy, taken because of the absence of pus and the nature of the tissue, will reveal the true nature of the condition. But the chronic stage presenting in the surgical clinic will almost certainly be regarded as a carcinoma. This rare but important breast condition is brought to the attention of surgeons in Britain, as more widespread appreciation of its clinical course and appearance will enable such cases to be discovered. Only elicitation and recognition of the previous course of events will arouse the suspicions of the clinician when confronted with a hard mass involving breast tissue around the age of

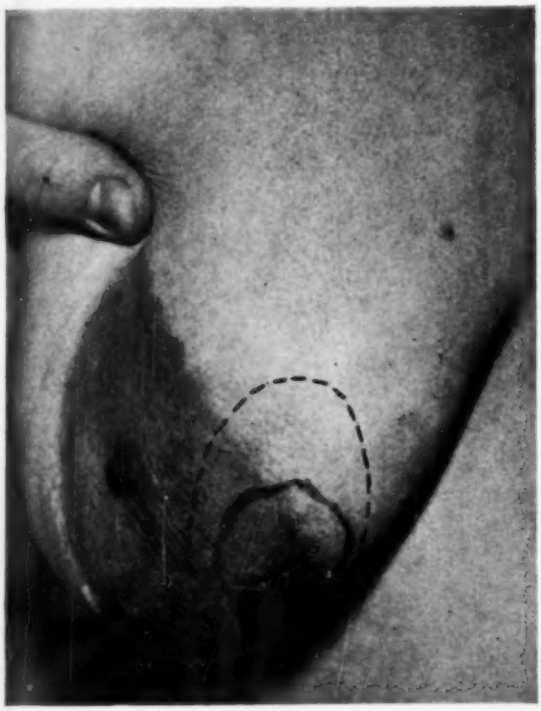

FIG. 583.—The area marked by skin pencil shows the extent of the lesion in the subacute phase, the dotted line representing its size in the acute phase.

40 and lead him to perform a biopsy. A plea is made, therefore, for biopsy and rapid paraffin section in a case with typical history, for only in this way will the radical ablation of an essentially benign breast be avoided.

The pitfalls facing the pathologist in diagnosing plasma-cell mastitis from a frozen section have been pointed out by M. Cutler (1949) to be (*a*) intense cellular hyperplasia of ducts apparently invading structures outside normal boundaries, and (*b*) swollen plasma cells simulating anaplastic malignant epithelial cells.

Treatment.—M. Cutler recommends irradiation of the subacute lesion and surgical excision of the residual mass in the chronic stage. Cromar (1949) also advocates removal of the mass. Observation of this present proven case of plasma-cell mastitis through all of its clinical stages suggests that the best treatment of this condition after diagnosis by microscopy is 'absolute inactivity'. Excision would not appear to be indicated as there is no convincing evidence of a relationship between it and carcinoma.

SUMMARY

1. The clinical picture and course of plasma-cell mastitis is not generally appreciated in this country.

2. The condition occurs in parous women at, or very close to, the age of 40. They have always breast-fed and any period of years may elapse between the last lactation and the appearance of the breast lesion.

3. In the acute phase the disease resembles an acute mastitis, which is in any case an unusual affliction in the woman about 40. The subacute phase resembles an abscess which has become attenuated under penicillin therapy, but the chronic phase mimics carcinoma closely. Plasma-cell mastitis is regressive, whilst carcinoma is progressive.

4. A plea is made for biopsy of a hard mass in the breast, when a typical history is obtained. Any risk thereform must be weighed against the possibility of ablation of a breast which is not the seat of cancer.

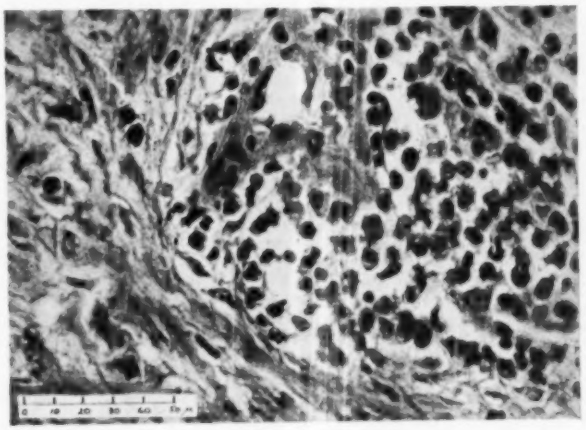

FIG. 584.—Low-power view. The field shows marked fibrosis and numerous typical plasma cells associated with a ductule. (× 37·5.)

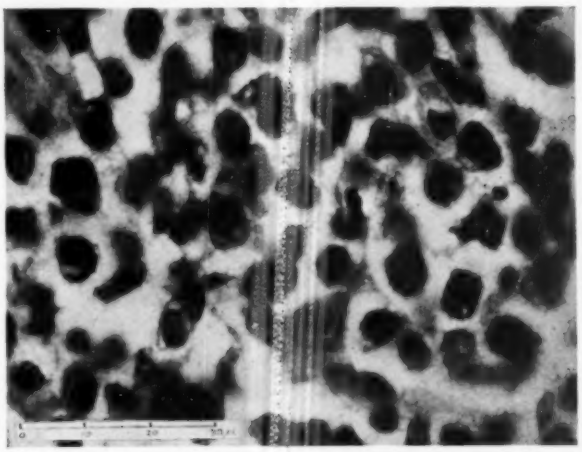

FIG. 585.—High-power view, showing the eccentric nucleus and peripheral chromatin arrangement of the plasma cells. (Oil immersion, × 1250.)

5. The lesion does not require any treatment, because the mass disappears and because there is no convincing evidence that it is precancerous.

6. It is suggested here that plasma-cell mastitis is due in the first place to trauma to the breast which damages the duct epithelium and permits extravasation of duct contents into the periductal tissue. The specific reaction of plasma cells is provoked by products of fatty acids from the ducts, but it is possible that this is determined by the waning progesterone influence on the breast at or after the age of 40.

I am particularly grateful to Dr. A. C. Counsell, who was responsible for the immediate recognition of the condition by rapid paraffin section and who has given me advice on its pathology. My thanks are due to Mr. J. Scholefield for his kind advice and for permission to publish the case; to Mr. Vinten for the photograph; and to Mr. Cain, of Aberdeen University Anatomy Department, for the micro-photographs.

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INTERNAL SUPRAVESICAL HERNIA

REPORT OF A CASE PRESENTING WITH BLADDER SYMPTOMS

BY D. R. BARNES AND B. J. DREYER
GROOTE SCHUUR HOSPITAL, CAPE TOWN, SOUTH AFRICA

THIS rare type of hernia commences as a peritoneal protrusion through the supravesical fossa. This fossa is bounded by the obliterated umbilical artery laterally, the urachal ligament medially, and the fundus of the bladder inferiorly. Thus there are two supravesical fossæ, one on each side of the urachal ligament as shown in *Fig.* 586. If the sac tracks deeply into the cave of Retzius or into the paravesical space, it is known as an internal supravesical hernia. If the sac presents in the hypogastric, inguinal, or femoral regions, it is known as an external supravesical hernia.

The presenting symptoms in the majority of the recorded cases have been those of intestinal obstruction; in many reports bladder symptoms were noted, but were of minor degree. The case report which follows is of interest as the presenting symptoms were urological.

CASE REPORT

J. R., a coloured male, aged 68, was first seen on Jan. 21, 1951.

HISTORY.—In 1947 he had an attack of lower abdominal pain of sudden onset, associated with an intense desire to micturate. He had great difficulty in voiding, associated with marked frequency. After twelve hours all the symptoms were suddenly relieved.

He was quite well until October, 1950, when he noted increased frequency and difficulty in micturition.

These symptoms slowly progressed, and on Jan. 21, 1951, he developed severe colicky lower abdominal pain associated with great difficulty in passing urine. He had not vomited and had passed flatus.

ON EXAMINATION.—Temperature 97·4°, pulse 90, respirations normal. The tongue was furred but moist. There was slight central abdominal distension. Tenderness was noted on deep palpation in the hypogastrium; the bladder was not palpable. On rectal examination the prostate was slightly enlarged; above the prostate and on the right side of the bladder a soft, smooth, tender swelling was felt.

A catheter was passed and 4 oz. of clear urine was withdrawn. The rectal examination was repeated and the physical signs were unchanged.

During the next twelve hours the abdominal pain became more severe and he started to vomit.

He was admitted to Groote Schuur Hospital on Jan. 22. On examination his tongue was now dry and furred. The central abdominal distension had increased and the tenderness in the hypogastrium was still present. There were no external herniæ and tests for obturator hernia were negative. The findings on rectal palpation were unchanged. An enema did not produce flatus or fæces.

SPECIAL INVESTIGATIONS.—(1) Leucocyte count—6500 per c.mm. (2) A straight radiograph of the abdomen showed dilated small bowel with multiple fluid levels.

The pre-operative diagnosis was intestinal obstruction, probably due to an internal hernia.

The significance of the urinary symptoms and of the swelling palpated per rectum was not appreciated.

AT OPERATION (B. J. D.).—The abdomen was opened by a left paramedian incision. The small bowel was distended, but a distal collapsed portion was traced to a hernial opening in the right supravesical fossa. The lateral margin of the neck of the hernial orifice was incised and 8 in. of strangulated but viable small bowel was withdrawn. Exploration of the sac indicated that it was firmly adherent to the right lateral wall of the bladder; it was therefore not removed. The hernial orifice, which admitted three fingers, was closed with interrupted silk sutures and the abdomen was closed in layers.

The patient made an uneventful recovery, and his bladder symptoms have been completely relieved.

DISCUSSION

Miller (1947) reported the forty-first case of this rare type of hernia. In reviewing the subject, he pointed out that a pre-operative diagnosis should

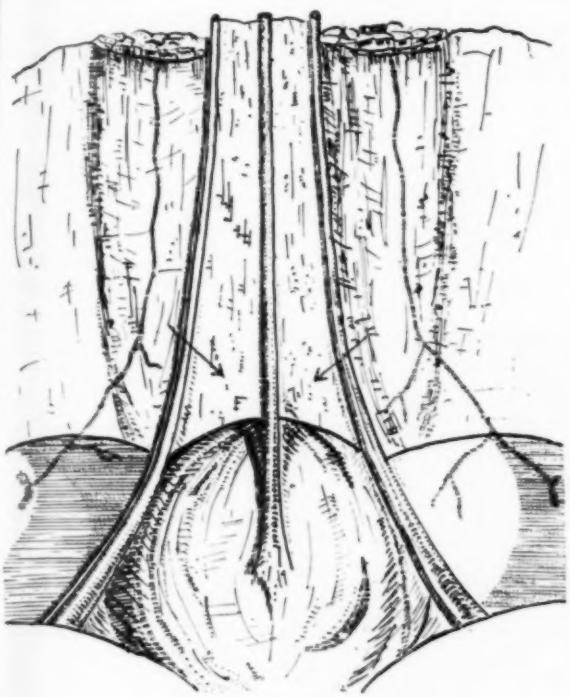

FIG. 586.—The supravesical fossæ.

be possible in a number of cases, as the signs and symptoms are characteristic. The usual picture is an elderly male presenting with intestinal obstruction and associated bladder symptoms. The significant signs are hypogastric tenderness without the physical signs of bladder distension, combined with the presence of a soft, smooth, tender, paravesical mass on rectal palpation. We would add that this mass should persist after emptying the bladder. In the case described above, all the significant signs and symptoms were present.

A correct pre-operative diagnosis has been made once only. Blum (1904) cystoscoped his patient and saw the bladder deformity caused by the extravesical swelling; he diagnosed a supravesical hernia. Miller (1947) and Warvi and Orr (1940) have credited Fromme with this achievement; however, Fromme (1908) states in his article that the pre-operative diagnosis in his case was strangulated inguinal hernia of the Richter type.

It is possible that in some cases the condition may not be recognized at operation. Mr. L. B. Goldschmidt (1952) recalled treating a patient who presented with retention in whom catheterization withdrew a small amount of urine but did not relieve his pain. A suprapubic incision was therefore performed. At operation difficulty was experienced in locating the bladder, owing to the fact that the peritoneum could not be stripped upwards. During the manipulations a peritoneal pocket was opened and congested small bowel presented. As the condition of the patient was very poor at this stage, the bowel was reduced and the peritoneum was hastily repaired. He made a good recovery and the urinary symptoms were relieved. This was almost certainly a supravesical hernia.

The majority of the recorded cases have presented with intestinal obstruction and have been submitted to an emergency laparotomy. The strangulated portion has always been small bowel. After reduction of its contents, a fairly large sac remains, which is usually closely adherent to the bladder. Experience has shown that removal of the sac is unnecessary as simple closure of the neck of the sac is sufficient to produce a cure. No recurrences have been recorded following this simple procedure.

We are indebted to Mr. G. Sacks, under whose care this case was admitted; to Dr. de Wet, Medical Superintendent of Groote Schuur Hospital, for permission to report the case; and to Dr. Whitaker for the illustrations.

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SHORT NOTES OF RARE OR OBSCURE CASES

ANNULAR PANCREAS

By IAN W. MacPHEE

DEPARTMENT OF SURGERY, UNIVERSITY OF LIVERPOOL

ANNULAR pancreas, though recorded from time to time, is an infrequent cause of symptoms. McNaught (1933) has summarized the 40 reported cases to that date, and Stofer (1944) has listed another 7. Bickford and Lloyd Williamson summarized in 1951 the total cases reported as 58, they themselves adding 1 case, and Anderson and Wapshaw reported a case at the same time. During 1951 Wakeley reported details of 1 case, thereby recording 61 cases. These writers, however, had failed to note several other cases appearing in the literature about that period. Briefly these were: Orts and Dueñas (1950)—1 case; Baker and Wilhelm (1950)—1 case; Dubost, Allary, and Sullivan (1950)—1 case; Ravitch and Woods (1950)—3 cases; Haden (1950)—1 case; Conroy and Woelfel (1951)—2 cases; and Payne (1951)—1 case. With the case described here, the total number of recorded cases appears to be at least 72.

FIG. 587.—Barium radiograph showing narrowing of the pars descendens duodeni.

FIG. 588.—Radiograph seven years after resection of annular pancreas.

It would appear, therefore, that the condition is being reported in recent years with some frequency, and probably more than 72 cases have now been reported. Whereas Wakeley remarks that only 17 of the 58 cases had presented with clinical symptoms of the condition, almost all the above cases were detected following the onset of gastro-intestinal disorders. The purpose of the present report is to present details of a case which has been observed for eight years following operation for the relief of the condition, and to discuss the treatment.

PATHOLOGY

The pathology and developmental anatomy of the condition has been adequately described previously by other observers. The essential feature is the presence of a ring of pancreatic tissue extending from behind, and encircling the duodenum anteriorly. The ring is usually narrowest and weakest on the anterior duodenal aspect. The pancreatic tissue differs in no way from normal, unless it has been the seat of intercurrent disease. If causing symptoms, the duodenum and stomach are commonly dilated and hypertrophied above the point of the obstruction. As Dubost, Allary, and Sullivan (1950), and Ravitch and Woods (1950) indicate, and as this present report will demonstrate, the duodenum itself may actually be stenosed within the cuff or ring of pancreatic tissue. In this event, severance of the pancreatic ring does not suffice to relieve symptoms, as was formerly suggested by many writers. The greatest degree of stenosis is usually just proximal to the ampulla of Vater, accounting for the rarity of jaundice. Anderson and Wapshaw have, however, reported such a case, indicating that the common bile-duct may suffer compression.

CLINICAL FEATURES

The case usually presents as one of duodenal obstruction. The condition is not liable to be diagnosed as carcinoma of the pancreas even in the presence of jaundice, but may well be mistaken for chronic duodenal ileus, as was the subject of the present report. Recurrent post-prandial vomiting is the rule, usually after every meal, unlike true pyloric stenosis. The condition usually appears to present in early adult life with an insidious onset. Unlike chronic duodenal ileus, relief is rarely obtained when the patient lies down. Symptoms are curiously uncommon in childhood and adolescence, which is

surprising in the presence of such a developmental abnormality.

The vomiting is usually associated with epigastric pain, and the condition is, in consequence, frequently mistaken for peptic ulcer. The cases reported by Orts and Dueñas (1950) and Baker and Wilhelm (1950) were actually associated with ulcer, the first in the duodenum and the latter in the stomach. The fact that the pain is not relieved by alkali may be of some help in diagnosis. As with pyloric stenosis, however, achlorhydria is the rule, and blood may be detected in the gastric aspirations.

CASE REPORT

S. W., male, aged 26, was first seen in December, 1943. At that time he complained of epigastric pain commencing 1½ hours after a meal, and associated with vomiting. The vomiting frequently relieved the pain.

He had been first aware of the complaint four years previously, and the condition had become progressively worse. The fractional test-meal demonstrated an achlorhydria. Three years previously, duodenal ulcer having been diagnosed, the patient had been discharged from the Army in consequence.

A barium meal in January, 1944 (*Fig.* 587), showed a grossly dilated stomach and first part of the duodenum. A constriction can be detected in the descending portion of the duodenum.

A laparotomy was performed by Professor Charles Wells, and a distended stomach and first part of duodenum were observed, the constriction of the second part being due to an annular pancreas. The narrow anterior neck of pancreas was dissected out and excised. No stenosis of the duodenum was then evident.

The patient was seen again in February and in March, when he still complained of occasional vomiting and some pain of a colicky type.

Since that time he has been unable to eat large meals, and has had occasional attacks of pain and vomiting.

In December, 1950, he began to vomit immediately after meals. This vomiting was associated with abdominal pain. In January, 1951, a barium meal (*Fig.* 588) showed some thickening of the stomach and duodenal mucosa, but no delay in gastric emptying. A constriction is still evident, however, in the second part of the duodenum. As the patient is now under the care of another surgeon, the decision to undertake further treatment remains with him. At present, he does not consider further surgical intervention necessary.

TREATMENT

The surgical treatment of the condition may either be by resection of the obstructing agent, or a by-pass procedure. Resection is usually recommended in adults. In the 3 cases reported by Ravitch and Woods (1950) and in the case described by Payne (1951), however, the duodenal stenosis was not abolished by resection of the constricting pancreatic tissue. Payne was able to demonstrate X-ray evidence of persisting obstruction associated with recurrence of symptoms four months after operation. As the case-history detailed here has shown, symptoms of recurrent obstruction may be postponed for many years, and though never severe enough to require further surgical intervention, may certainly be troublesome to the patient.

It would seem wise, therefore, if excision of the annular pancreas is practised, and if any degree of duodenal stenosis is evident, to eliminate it by performing longitudinal duodenotomy and transverse suture.

The writer has no experience of by-pass operations such as duodenojejunostomy, gastrojejunostomy, or partial gastrectomy. In a study of chronic duodenal ileus treated by by-pass operations, however, (Wells and MacPhee, 1952) he has observed that the operation of gastrojejunostomy does not necessarily relieve the distension of the duodenum, and consequently the tendency to pain and occasional vomiting.

SUMMARY

A case of annular pancreas treated by resection of the constriction is described. The course of the patient during the next eight years is discussed. It is suggested that division and resection of the constricting pancreas by itself may not be sufficient.

I am grateful to Professor Charles Wells for permission to publish details of this case.

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INTRAPERICARDIAL DIAPHRAGMATIC HERNIA

BY V. S. BROOKES

DEPARTMENT OF SURGERY, QUEEN ELIZABETH HOSPITAL, BIRMINGHAM

IN the traumatic type of diaphragmatic hernia caused by indirect injury, such as severe compression of the abdomen, the left dome of the diaphragm is most frequently involved, the right side being partially protected by the liver. The hernia may be either: (*a*) A complete rupture of all layers of the diaphragm with prolapse of the abdominal contents into the pleural cavity, without a peritoneal sac and like congenital herniæ through the pleuroperitoneal canal; or (*b*) A tear of the muscular fibres only, with

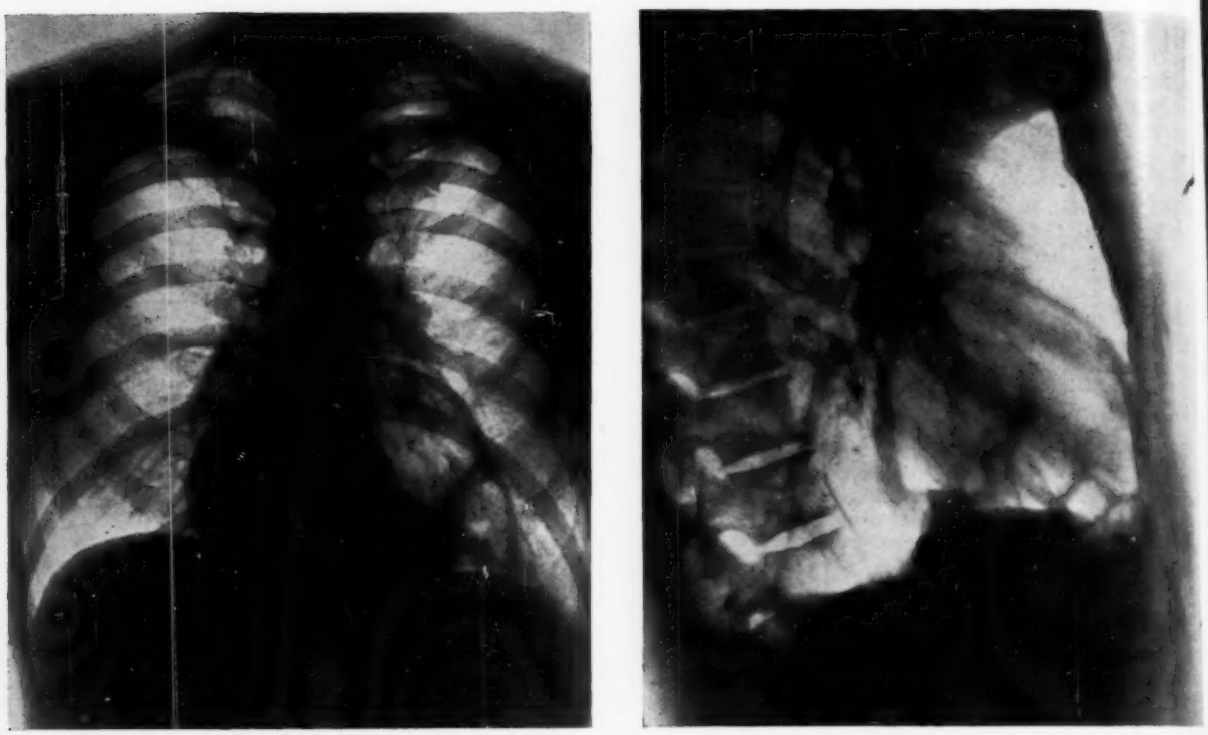

FIG. 589.—Pre-operative anteroposterior and lateral radiographs, showing intrapericardial diaphragmatic hernia.

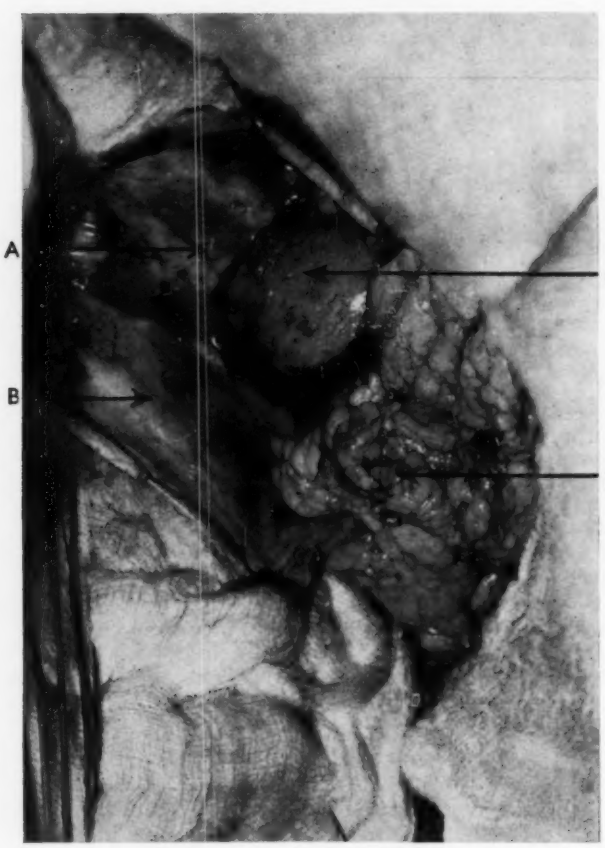

FIG. 590.—Photograph taken at operation, showing stomach and omentum in the pericardial sac. A, Heart; B, Reflected pericardium; C Omentum; D, Stomach.

FIG. 591.—Photograph showing diaphragmatic defect after the stomach had been returned to the abdomen. A, Heart; B, Reflected pericardium; C, Sutures through divided edge of omentum; D, Defect in diaphragm.

eventration of the peritoneum as a sac through the tear. A case has recently been seen in which the hernia was of the first type and was of particular interest because it had involved the central portion of the diaphragm, with prolapse of part of the abdominal contents into the pericardial sac. Intrapericardial diaphragmatic herniæ do not appear to be mentioned in the literature.

CASE REPORT

HISTORY.—A man, aged 48, was admitted to the Queen Elizabeth Hospital in April, 1952, with a history that he had been involved in a road accident one year before, when he was knocked down by a bus. He was treated at the time at another hospital for fractured left clavicle, fractured second and third ribs, and a bruised left thigh. He said that the wheel of the vehicle also caused considerable compression of his abdomen. After treatment for his fractures he was allowed to leave hospital, but was again admitted a few days later complaining of severe breathlessness and a cough with sputum. At that time he had gross moist sounds in both lungs and his sputum was copious but not blood-stained. He was treated with penicillin and sulphamezathine and rapidly improved. During this second stay in hospital he developed marked bruising of his left thigh, scrotum, and lower abdominal wall, and an abscess formed in the left thigh which had to be opened. Radiography of his chest at this time showed a left diaphragmatic hernia, with the body of the stomach in the thorax but the cardia in the abdomen.

During the intervening year before admission to the Queen Elizabeth Hospital he complained of gurgling noises in his chest and a feeling of fullness after even a small meal; if he took a large meal it was invariably followed by severe palpitations, and palpitations and shortness of breath also followed exercise. He had not vomited on any occasion.

X-ray examination of the chest on admission showed a hernia in the left side of the chest lying alongside the heart shadow. The lateral film showed that the hernia was anterior in position and a barium swallow showed that the content of the hernia was stomach. The cardia and pylorus were below the diaphragm whilst the body of the stomach was in the chest. (*Fig.* 589.)

AT OPERATION.—A left thoracotomy was performed through a posterolateral incision, with excision of the seventh rib. There were many avascular adhesions over the left lower lobe and these were divided. At first no hernia was detected, but the pericardium was very prominent and there appeared to be a great increase of fat in the anterior end of the pericardiophrenic angle.

On dissection this fat was found to be greater omentum which had prolapsed into the pleural cavity through a small hole, 1 in. in diameter. The omentum was adherent to the defect and was blocking it; it was mobilized and returned to the abdomen. The pericardium was palpated and gurgling noises suggestive of bowel were heard. A vertical incision in the pericardium was made behind the phrenic nerve. The stomach and most of the greater omentum were found inside the pericardial sac, the omentum being very adherent to the great vessels and the stomach loosely adherent to the visceral pericardium. (*Fig.* 590.) As is often the case in diaphragmatic hernia, the stomach had rotated in its long axis so that the greater curvature lay uppermost, only the body being in the pericardium, the cardia and the pylorus remaining in the abdomen. There was no peritoneal sac, the pericardium and peritoneum being continuous. A large defect, some 4½ to 5 in. from left to right and 2½ to 3 in. from front to back, was present in the diaphragm below the pericardium. The defect was continuous, at its left end, with the small opening into the left pleural cavity, through which the omentum had prolapsed. The upper surface of the liver presented in the posterior part of the defect and the lower border of the heart was loosely adherent to this area of the liver. The stomach and greater omentum were mobilized and returned to the abdomen. The heart was freed from the upper surface of the liver and the latter displaced downwards. The right edge of the defect was then completely defined and it ended just to the left of the inferior vena cava. (*Fig.* 591.) The edges of the defect throughout its entire extent contained firm muscle and fibrous tissue. Interrupted thread sutures (size 40 thread) were placed in an anteroposterior direction through the edges of the defect so that when they were tied the defect was firmly closed. Since the pericardium was very voluminous, a flap from the left side of it was turned down to reinforce the suture line and was secured with fine sutures. The rest of the pericardium was loosely closed around the heart and the thoracotomy wound was closed without drainage.

FIG. 592.—Post-operative lateral radiograph.

The post-operative course was uneventful, the gurgling noises in the chest disappeared and the patient was able to eat a large meal without any feeling of distension or any palpitation. A post-operative barium swallow showed the stomach now to be in its normal position. (*Fig.* 592.)

I wish to express my gratitude to Professor F. A. R. Stammers and Mr. A. L. d'Abreu for their advice and permission to publish this case. I would also like to thank Mr. T. F. Dee for preparing the photographic prints.

CAVERNOUS ANGIOMA OF THE MEDIASTINUM IN A CHILD

By J. L. EMERY and S. A. DOXIADIS

CHILDREN'S HOSPITAL, SHEFFIELD

CAVERNOUS angiomas of the mediastinum are infrequently reported and clinically rarely considered. A case is reported here of a boy having a circumscribed angioma of the upper mediastinum.

CASE REPORT

The patient, a boy, was born in June, 1943, the second child of healthy parents. There was no abnormality during pregnancy, delivery, neonatal period, and infancy. When aged 4 years (August, 1947) he was admitted to the Children's Hospital, Sheffield, for repair of an inguinal hernia. He had never complained of any general or respiratory symptoms and his general condition and nutrition were normal. The routine tuberculin skin test was found to be positive. A radiograph of the chest (*Fig.* 593) showed an unexpected opacity of the upper half of the left lung. There were physical signs in his chest consistent with consolidation of the left upper lobe, also displacement of his trachea to the right. During the following four months the physical signs in his chest remained the same and his general condition continued to be good. The sedimentation rate was normal, with only one slightly raised reading, which was attributed to an intercurrent infection. His chest was aspirated four times. In the first (September, 1947) only 1 ml. of straw-coloured fluid was obtained. In the second (October, 1947) clear yellow fluid was obtained at the beginning and it quickly became blood-stained. In the third (November, 1947) 20 ml. of heavily blood-stained non-clotting fluid was obtained, and in the fourth (November, 1947) the fluid was once again blood-stained. Guinea-pigs inoculated from the first three aspirations were uninfected.

In December, 1947, the patient was discharged home for Christmas. All trace of the patient was lost until he was re-admitted in October, 1951, now aged 8 years. He had apparently been well until three weeks before admission, when he developed a dry tickling cough which persisted until admission. He lost his appetite, became listless, and became breathless easily. Two weeks before admission his mother noticed swelling of his face and eyelids, a small hard lump in the right side of his neck, and prominent veins on the upper part of his chest. On Oct. 26 he looked ill but without obvious respiratory distress. There was a right-sided Horner's triad. The right side of his neck was swollen and in the centre of this diffuse soft swelling a small hard mass was palpable. The veins on the right side of the neck and of the upper part of the chest were distended. The trachea was displaced to the right and the cardiac impulse could be felt in the midline below the xiphisternum, and at the right of the sternum. The percussion note was stony dull over the left superior two-thirds of the left hemithorax and the breath-sounds were absent over the whole area. The radiograph showed a round opacity in the upper two-thirds of the left thorax and the upper mediastinum (*Fig.* 594). The heart and trachea were displaced to the right. Screen examination confirmed this and also showed straightening of the œsophagus when filled with

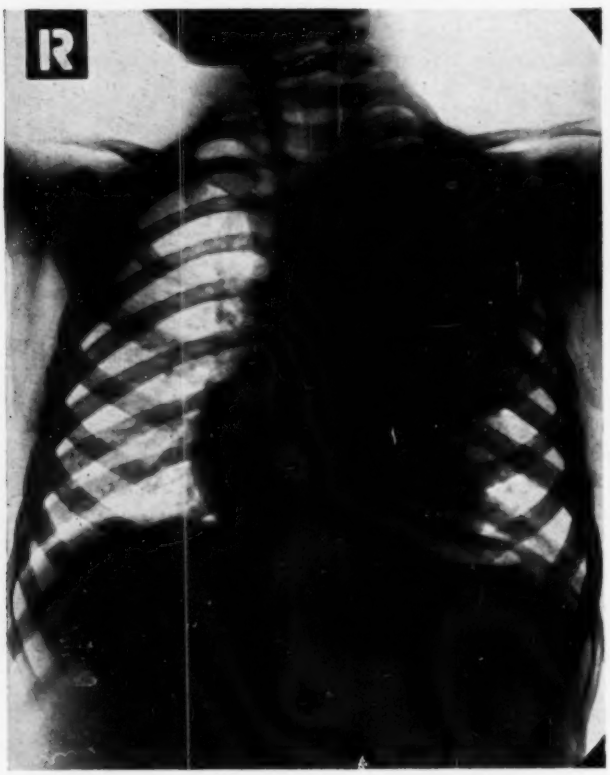

FIG. 593.—Radiograph taken in August, 1947, when the child was 4 years old.

FIG. 594.—Radiograph taken in October, 1951, when the child was 8 years old.

barium. The œsophagus was also displaced to the right. On a bronchoscopy the trachea appeared slit-like in its middle and lower third, as if by external compression. The right main bronchus appeared normal. The left main bronchus was constricted below the carina as though by external pressure. There was some mucopus but no obvious infiltration.

After the bronchoscopy the patient had a very troublesome cough and stridor and 12 hours later an emergency tracheotomy was performed. This did not alleviate the symptoms and he died within two hours with signs of gross dyspnœa.

ABSTRACT FROM NECROPSY REPORT.—There was a well-circumscribed irregular mass approximately 14 × 16 × 8·5 cm. situated in the upper left mediastinum (*Fig.* 595). It extended upwards almost to the thyroid gland; anteriorly, it compressed the veins from the neck and the thymus; posteriorly, the tumour covered, but did not surround, the stellate ganglion. Medially a prolongation of the tumour passed behind the thymus and in front of the trachea and great vessels. It terminated in front of, but not compressing, the right stellate ganglion. Laterally the pleura was lifted and the underlying left upper lobe was collapsed. The upper-lobe bronchus did not appear to be obstructed or involved in the tumour.

Microscopically the tumour consisted of large blood-vessels containing both old and fresh coagulated blood. Extensive sections were taken from many parts of the tumour but no tissue other than blood-vessels and mature connective tissue was seen. The tumour appeared histologically benign. The thymus, thryoid, pleura, sympathetic ganglia, and great vessels of the upper mediastinum were not infiltrated and no abnormalities were found in any organs of the body other than the lungs, which showed changes of asphyxia.

ANATOMICAL DIAGNOSIS.—A large discrete cavernous angioma situated in the upper left mediastinum producing collapse by displacement of the left upper lobe of the lung and compressing the veins from the neck and stellate ganglion. Death was associated with bronchoscopy.

DISCUSSION

Angiomas of the mediastinum are rare tumours. Geschickter and Keasbey (1935), in a review of 560 angiomas, do not record any in the mediastinum; similarly Pack and Miller (1950), in a more recent review of angiomas, do not mention their occurrence in the mediastinum. Bergstrom (1945) reported 2 cases, both occurring in newborn children, one with a diffuse angioma of the diaphragm and pericardium and the other angioma apparently arising in the thymus and rupturing into the left pleural cavity. Döderlein (1938) records an angioma of the diaphragm in a premature child who died soon after birth. Adams and Block (1944) reported one case in a man, aged 34, which was successfully removed surgically. Schlumberger (1951) reports a mediastinum angioma in a man aged 26; the tumour was composed of vascular spaces distended by blood and separated by a fibrous tissue. He states that the literature contains only 3 such cases. He also mentions a tumour of similar appearance removed from the anterior mediastinum of a 17-year-old boy which later recurred locally as a malignant teratoma.

Whether angiomas of the mediastinum should be considered as separate from the other mixed tumours occurring in the mediastinum or as potential

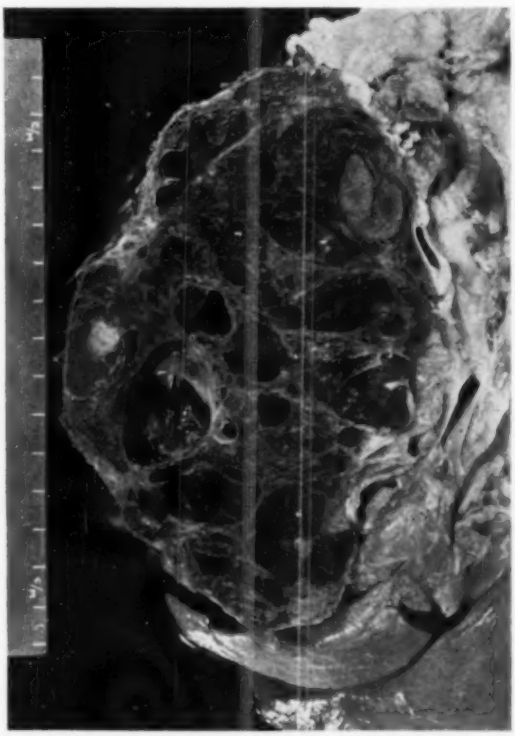

FIG. 595.—The tumour, cut after fixation, showing the cystic spaces and the relationship of the tumour to the lung.

mesenchymomas (Stout, 1948) it is difficult to say, but the general appearance and structure in the present child suggests that operative removal could have resulted in a complete cure.

SUMMARY

A benign well-demarcated cavernous angioma of the mediastinum in a young child is reported. Death was associated with bronchoscopy.

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AN UNUSUAL PHYTOBEZOAR WITH MULTIPLE COMPLICATIONS

By H. B. YOUNG, Wolverhampton

Bezoars, foreign bodies which take on shape after being swallowed, are well known but always surprising occurrences. DeBakey and Ochsner (1938) state that of a total of 311 collected cases of bezoars and concretions, 55·3 per cent were trichobezoars (hair-balls) and 40·4 per cent were phytobezoars (food-balls). In the latter, 29·5 per cent were persimmon bezoars and 10·9 per cent other bezoars.

The interesting points about the case recorded below were: (1) It belonged to the small group of 'other' bezoars, and was due to nuts, which had caused gastric ulcers—an accompaniment of such phytobezoars in only 6·5 per cent of cases, according to the above authors; (2) The shape of the bezoar outlined the main limbs of a large gastro-ileal fistula, despite which the patient's nutrition was extraordinarily good; (3) The unusual symptomatology due to the complications which also necessitated more extensive surgery than usual.

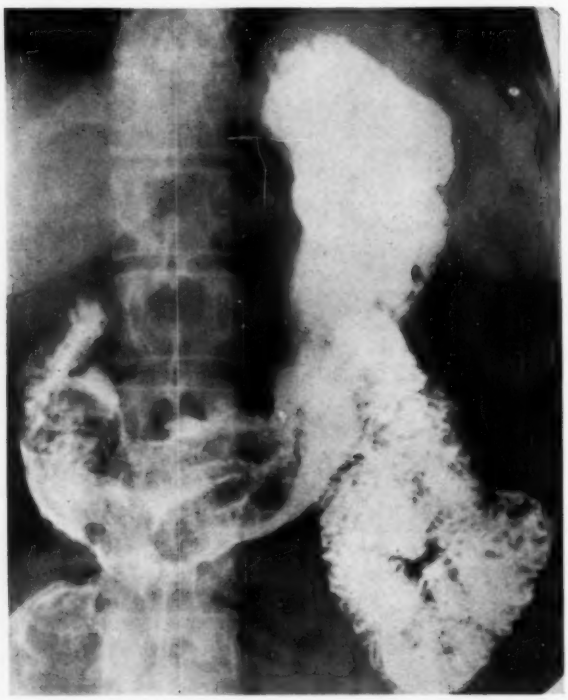

Fig. 596.—The radiograph. This seemed to confirm the clinical diagnosis of pyloric carcinoma.

CASE REPORT

A married woman, B. B., 46 years of age, complained of epigastric ache for some five months. Apart from an operation for an ovarian cyst four years previously, she had had no illnesses. The pain began gradually, as 'indigestion'. It came on in attacks lasting about half an hour at a time, commencing without relation to meals, but always ending suddenly in the left axillary region. She had some acid regurgitation but no vomiting or hæmatemesis. Anorexia was, however, present, and she had lost weight over the last year or so. In the last month the epigastric discomfort had eased, but she was now troubled with pain in the left lumbar region, which became severe when she lay down.

On Examination.—A well-coloured, well-covered middle-aged woman. Abdominal examination revealed the presence of a definite, though ill-defined, slightly tender non-mobile mass in the right epigastrium. Clinically she was diagnosed as having extensive carcinoma of the stomach, and a barium meal X-ray examination (*Fig.* 596) confirmed this. She was put on the waiting list for early exploration.

At Operation (May, 1952).—A left paramedian incision revealed an apparently stony hard mass in the thickened pyloric antrum of the stomach with the colon and several coils of ileum adherent to it. All were fixed together, but not so markedly to the posterior abdominal wall. No glands or hepatic or distant secondaries were found. The picture seemed that of a carcinoma with extensive local invasion, though it was felt to be rather sharply defined to be 'just right'. Resection was begun with a view to removal of all the affected tissues *en bloc*. On transection of the duodenum it was found that the forceps on the swab over the gastric end had slipped a little, permitting a hard, black, but green dappled object, outling the pylorus, to protrude. The real nature of the condition was immediately apparent (*Fig.* 597). Attempts, however, to remove the bezoar were unsuccessful and it was seen to be 'star' or 'staghorn' in shape, the limbs caught in those of a fistula.

Fig. 597.—The phytobezoar protruding from the pyloric end of the stomach after transection of the duodenum.

This was dissected free and the foreign body removed (*Fig.* 598). The fistula was found to have eroded two loops of ileum. The deficiencies in the ileum were considerable and ragged and were closed as nearly transversely as possible and the affected segment excluded by a lateral anastomosis, 2½ ft. above the ileocæcal junction to a point within 6 in. of it. A large ulcer could be palpated in the stomach proximal to the fistula and so a Billroth I partial gastrectomy with moderate removal of stomach was carried out.

Examination of the bezoar suggested that perhaps it had occupied the pyloric end, caused the fistula, extended into it, back up into the stomach, where peristalsis curled the proximal end back, and finally through the fistula again. It appeared homogeneous at first, but separated out, as seen in the photograph, on palpation.

PATHOLOGY.—Pathological examination of the stomach was as follows :—

Macroscopical.—A small polyp ½ cm. in diameter presents attached to the mucosa, an ulcer in the body of the stomach, and one large gland.

Microscopical.—Section shows " quite a large papilloma with much hyperplasia of the peptic glands. No malignancy seen. Ulcer shows no malignant change. Gland shows reactive changes only ".

PROGRESS.—The patient was interviewed during her convalescence, which was uneventful apart from a slight discharge from the wound, and found to be of normal, and indeed good, intelligence and personality. She had no personal or occupational habits to account for hair or wool being ingested. However, more careful discussion of her dietary likes and dislikes revealed the cause—nuts, of all kinds. For two years she had had a great and insatiable desire for them. Indeed, no one ever left the house without returning with a packet of them for her. She seemed surprised to know that they might have caused her upset, but offered to desist from them and to warn her daughter who, because of this environment of nuts, was beginning to acquire a liking for them.

FIG. 598.—The phytobezoar after removal.

DISCUSSION

Re-survey of the cause in the light of the operative findings shows some doubtful points in the diagnostic chain of events and explains others. The barium in one film seems to surround the filling defect in the stomach and also to escape beyond the gastric confines at one place (*see Fig.* 596). The foreign body seems to have formed, caused an ulcer on the greater curvature of the stomach, which, like the one higher up, gave few symptoms till it began to erode the wall, when epigastric pain appeared—to be relieved on the formation of the fistula, but replaced by a wider extension of the inflammatory process causing peripancreatitis and a left-sided syndrome.

Her general condition was extraordinarily good for such an extensive and late carcinoma as it seemed to be. It was also unexpectedly good for the presence of a fistula from the stomach to within 6 in. of the ileocæcal valve. There must have been two streams of contents—one during the gastric phase, passing to the pylorus, and one during the intestinal phase, passing along the ileum—the streams separated by the bezoar which may have exerted some ball-valve action. The barium did pass on to the jejunum, as seen in the film. This was a safer mechanism than getting a small-bowel obstruction at the site of adhesion of stomach and ileum.

Some surgeons (e.g., Maingot, 1948) do not think gastric resection warranted in cases with ulcers associated with foreign bodies, as they are traumatic and heal when the cause is removed. In this case, however, little other course was open, as not only was there a fairly large ulcer (cavity over ½ in. in diameter) left in the stomach, but the fistulous opening was large and, of course, the duodenum had already been divided. The ulcers were chronic and surrounded by much induration. It is doubtful if they might not have been maintained by even the normal acidity. Further, here the papilloma might have proved to have been of more serious significance. Medical treatment would have been of no avail, of course, as the mass was not glutinous to the touch and extended into too many corners to be broken up by drugs. The death-rate under treatment by conservative means is stated to be about 50 per cent. DeBakey and Ochsner (1938) state that the operative mortality for phytobezoars was 2·1 per cent but rose to 18·7 per cent in the presence of ulceration and intestinal obstruction, making the condition one of considerable gravity, with a happy outcome by no means assured.

SUMMARY

An unusual phytobezoar due to nuts and causing papilloma of the stomach, a gastric ulcer, and a separate gastro-ileal fistula is described, and its various features discussed.

I have to thank Mr. W. R. S. Hutchinson, of the Royal Hospital, Wolverhampton, for permission to publish this case, and Mr. Paton, of the Photographic Department, for the photographs.

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REVIEWS AND NOTICES OF BOOKS

Cleft Lip and Palate. By W. G. HOLDSWORTH, M.B., F.R.C.S., Surgeon, Rooksdown House, Basingstoke; Consultant in Plastic Surgery, South West Metropolitan Hospital Region; Honorary Plastic Surgeon, Dr. Barnardo's Homes. With a Foreword by Sir HAROLD GILLIES, C.B.E., F.R.C.S. $7\frac{1}{4} \times 9\frac{3}{4}$ ins. Pp. 126 + xi, with 75 illustrations. 1953. London; Heinemann. 35s.

THIS book is a praiseworthy attempt to bring together in easily accessible form most of what is known of the pathology and treatment of cleft lip and palate. It is the first serious effort in this field in England since the work of Berry and Legg and Lane thirty-five years ago. The author does not lay claim to any original technique and modestly refrains from advancing his own statistics, though his experience might well have led to him do so. It is evident from the critical analysis which he makes of widely practised procedures and techniques that he knows what he writes about.

The book follows conventional lines and begins with a section on the anatomy and development of the deformity. The style here is rather jerky and difficult to read and there are mistakes in spelling which require correction. Chapters on the technique of cleft lip and palate repair are excellent and show a fine discrimination between what is sound common surgical sense and what strives for effect, between the simple types of primary repair favoured in England and the more complicated varieties associated with Transatlantic surgeons. He favours in general simple closure of the lip by Thompson's method at six months together with closure of the alveolar defect after Veau. Six months seems to err on the conservative side.

The palate is repaired by a modified Langenbeck technique at twelve months. Good descriptions are added of all other recognized techniques together with a critical appraisal of each. Immediate post-operative care is well described. Secondary operations are less adequately dealt with and dental treatment is discussed in one paragraph. These defects will no doubt be remedied in future editions, for the book will be popular with students facing higher examinations while it will also find a worthy place on the plastic surgeon's shelf.

Surgery in World War II: The Physiologic Effects of Wounds. By The Board for the Study of the Severely Wounded, North African Mediterranean Theater of Operations. $6\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 376 + xiv. Illustrated. 1952. Washington, D.C.: Office of the Surgeon General.

THIS useful and practical monograph will be read with interest by all surgeons who are required to treat injured persons. To-day we live in a traumatic age; with the great increase of mechanical transport accidents and injuries are all too common. What the American Board for the Study of the Severely Wounded have done for the wounded in North Africa has opened the eyes of many practical surgeons. To mention only a few of the problems which this book elucidates: liver function in the severely wounded; renal function, crush syndrome, and the general pathology of traumatic shock. The value of whole blood versus blood substitutes is a problem we in this country are finding of real interest at the present time.

We are all pleased to see the name of Paul R. Hawley as a member of the Advisory Editorial Board. British surgeons owe him a great debt of gratitude for his keen co-operation with the medical profession in this country during World War II.

The Oesophagus and its Diseases. By EDDY D. PALMER, M.D., F.R.C.P., Lt. Col., Medical Corps, U.S. Army; Chief Gastro-intestinal Section, Walter Reed Army Hospital; Consultant in Gastroenterology to the Surgeon General. $6\frac{1}{4} \times 9\frac{1}{4}$ in. Pp. 553 + xiv, with 95 illustrations. 1953. London: Cassell & Co. Ltd. 93s.

THIS monograph dealing with the diseases of the œsophagus is of academic interest and appears to lack the practical approach, especially concerning the treatment of cancer of the œsophagus.

The author has set out to write an account of the œsophagus and its diseases based on American surgery, and takes little or no notice whatever of British surgeons who have done much to make surgery of the œsophagus safe.

In an extensive series of chapter references one misses the names of Grey Turner, Barrett, and other English surgeons who have written extensively on cancer of the œsophagus.

An Atlas of the Commoner Skin Diseases. By HENRY C. G. SEMON, M.A., D.M., Oxon., F.R.C.P. Lond., Consulting Physician for Diseases of the Skin, and former Lecturer to Post-graduates, Royal Northern Hospital. Colour photography originally directed by the late Arnold Moritz, B.A., M.B., B.C. Cantab. Fourth edition. $7\frac{1}{4} \times 9\frac{3}{4}$ in. Pp. 371 + viii, with 147 illustrations reproduced by direct colour photography from the living subject. 1953. Bristol: John Wright & Sons Ltd. 75s.

THIS well-known atlas contains some 147 plates reproduced by direct colour photograpy from living subjects. Dermatology is a difficult branch of medicine and it is only by seeing actual clinical cases that it can be demonstrated and remembered. This atlas will always remain as an excellent reference volume for the practitioner who wants guidance in dermatological cases. The coloured plates are beautiful and could not be bettered, and will go a long way to teach students such conditions as gummata, which are rarely seen to-day.

An excellent production.

Renal Cortical Necrosis and the Kidney of Concealed Accidental Hæmorrhage. By H. L. SHEEHAN, D.Sc., M.D., F.R.C.P., F.R.C.O.G., and H. C. MOORE, M.D., from the Department of Pathology, University of Liverpool. $7\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 186 + iv, with 64 illustrations. 1952. Oxford: Blackwell Scientific Publications. 35s.

THIS is an important book, for it deals primarily with the renal damage clinically observed in 67 fatal cases of concealed accidental hæmorrhage. For an extensive histological examination in these cases the authors consider that vascular spasm plays an important part in the causation of renal cortical necrosis and that the different degrees of renal damage depend on differences in the site and duration of this spasm. The aetiology of the spasm of the cortical arteries has not been clearly elucidated so far, but it is investigations such as Drs. Sheehan and Moore have undertaken which will no doubt solve this problem one day. These investigators report a few cases of renal cortical necrosis in children which may throw fresh light on the pathology of this interesting condition.

The value of this book is enhanced by the fact that the authors have carefully analysed all previously recorded cases of the condition from the extensive medical literature.

An important reference volume.

Recent Advances in Anæsthesia and Analgesia (including Oxygen Therapy). By C. LANGTON HEWER, M.B., B.S.(Lond.), M.R.C.P.(Lond.), F.F.A.R.C.S., Senior Anæsthetist, St. Bartholomew's Hospital; etc. Seventh edition. 5¼ × 8 in. Pp. 440 + viii. Illustrated. 1953. London: J. & A. Churchill Ltd. 30s.

THE seventh edition of this well-known book contains a new chapter which will interest all surgeons and anæsthetists as it deals with the introduction of induced hypotension. The author has written an admirable synopsis of the various measures now at our disposal for minimizing hæmorrhage during operative procedures, and expresses the opinion: "that the original enthusiasm for the hypotension method has waned, and it appears practically certain that in the near future it will be confined to a very limited sphere".

The arrangement of the other chapters is unaltered, but they have been enlarged and re-written, and contain details of many recent advances in anæsthesia, analgesia, and oxygen therapy.

The publishers are to be congratulated on the excellent production of the script and on the clarity of the numerous illustrations; these number 168, of which 52 are new. All consulting anæsthetists will agree that this book, first published in 1932, is one of the most valuable contributions to the literature of their specialty.

The Clinical Application of Antibiotics (Penicillin). By M. E. FLOREY, M.D., from the Sir William Dunn School of Pathology, Oxford. 6 × 9¾ in. Pp. 730 + xiv, with 115 illustrations. 1952. London: Oxford University Press. 84s.

THIS book by the wife of Sir Howard Florey is concerned with the clinical application of penicillin. It is stated in the preface that "it was proposed in Oxford that a number of workers should produce a book on antibiotics covering all aspects of their discovery, isolation, and chemical, bacteriological, and pharmacological characters, as well as their clinical use where this has been found possible. The enormous growth in the literature of the subject that took place in the years after the book was begun made it impossible to realize this proposal".

It is hoped later on to publish another book dealing with the clinical application of other antibiotics.

Two articles were published by Sir Howard Florey in the *Sunday Times* on December 7 and December 14, 1952, under the titles of "How we first made penicillin" and "New drugs, hopes and risks". These articles give the history of the discovery of *Penicillin notatum* by Sir Alexander Fleming in 1929 and the efforts to produce it on a commercial scale for therapeutic use by British firms of pharmaceutical chemists, and the workers of Oxford. He states "all the penicillin used for the first and encouraging trial of wounds in North Africa in 1943 was made by British firms in Oxford.

"British resources could not achieve a sufficiently large scale of production and in 1941 help was asked from similar firms in the U.S.A. which was immediately forthcoming, with the results we all know."

In 1945 Sir Alexander Fleming and Sir Howard Florey jointly were rewarded the Nobel Prize. Great help was given to them to test the therapeutic effect during the war and after by the late Sir Hugh Cairns.

A letter also appeared in the *Sunday Times* for Dec. 14, 1952, from Lord Webb-Johnson relating how nearly Lord Lister came to discovering the therapeutic effects of a mould Penicillium in 1871. There are now other "systemic chemotherapeutic agents" available, but none so safe for the patient as penicillin.

The first three chapters in this book consider the properties of clinical importance, general consideration of results, the complication of treatment, and method of administration.

The remainder of the book (500 pages) details the treatment with antibiotics of various diseases due to specific organisms. The amount of work which this has involved is indicated by the references to the literature made in each chapter under definite headings, and also the seventy-four pages devoted to the bibliography of publications dealing with the subject to date.

What it does emphasize is that from now on a bacterial diagnosis rather than a more anatomical one has become essential before any intelligent treatment with antibiotics can be carried out; in other words the bacteriologist has come into his own, and in addition it must be a well-trained and competent bacteriologist who controls the treatment.

The use of penicillin has had a very marked effect on medical and surgical practice. It has not only reduced the death-rate, but has enabled tissue to be preserved, and so reduced the number of cases requiring amputation and plastic repair; also by enabling early repair to be carried out on potentially infected wounds, the duration of acute infections has been shortened and so enabled function to be preserved more easily.

The author, however, sounds an important note of warning that there are grave dangers for the patient in the uncontrolled use of antibiotics. While it is true that penicillin is the least toxic, yet there are difficulties for the clinician inherent in the use of all antibiotics as regards the dosage and duration of treatment. Nurses who are continually giving penicillin are very apt themselves to develop a sensitivity owing to droplets from syringes getting on to their hands, and it would be a wise precaution if rubber gloves, not necessarily previously sterilized, should always be worn, but they must be sterilized afterwards.

It is impossible to review adequately a book such as this. It is a veritable encyclopædia for the 'use and abuse' of penicillin. It surely must take its place in the library of every hospital as a valuable work of reference, not only for the clinician but also the pathologist.

The author and publisher are to be congratulated on its format and method of presentation.

Pictorial Handbook of Fracture Treatment. By EDWARD L. COMPERE, M.D., F.A.C.S., and SAM W. BANKS, M.D., F.A.C.S., Northwestern University Medical School. Third edition revised with the assistance of CLINTON L. COMPERE, M.D., F.A.C.S. Illustrated by HAROLD LAUFMAN, M.D., F.A.C.S. 5¼ × 8 in. Pp. 424, with 223 illustrations. 1952. Chicago, Ill.: The Year Book Publishers Inc. 56s.

THIS volume is aimed at providing the isolated American general practitioner with an up-to-date, reliable, and succinct guide in the treatment of those fractures with which he may be faced. Its general plan and contents are for the most part good, but, in view of its avowed object, perhaps more space could have been devoted to the detailed treatment of recent injuries and less to the problems of late reconstruction, which are hardly in the province of the general practitioner surgeon.

There are one or two surprising statements: Arterial obstruction is not considered in relation to Volkmann's ischæmic contracture, which is ascribed to venous compression—a view abandoned some years ago. Excision of the styloid process of the radius as the treatment of non-union of the carpal scaphoid, and the use of the well-leg tractor are both procedures which have not gained wide acceptance. Nor has skeletal traction in the treatment of finger and hand fractures.

This book will not appeal to many readers in Great Britain, for it lies too much in the region of the 'in-between'—too large for a small fracture monograph, and too small for a work of reference. Judging by its past success, it will continue to be popular amongst the 'occasional' fracture surgeons in the United States.

Anatomy of the Autonomic Nervous System. By G. A. G. MITCHELL, O.B.E., T.D., M.B., Ch.M., D.Sc., Professor of Anatomy and Director of the Anatomical Laboratories in the University of Manchester. With a Foreword by Sir JAMES LEARMONTH, K.C.V.O., C.B.E., Ch.M., LL.D., F.R.C.S. (Edin.). $6\frac{7}{8} \times 9\frac{7}{8}$ in. Pp. 356 + xvi, with 131 illustrations, many in colour. 1953. Edinburgh: E. & S. Livingstone. 55s.

THIS book certainly meets a great need, for surgeons to-day require more detail concerning the autonomic nervous system if their many and varied operations are to be successful. Professor Mitchell has studied his subject carefully for many years and has published many excellent papers on the sympathetic nervous system, and this book is the sum and substance of his researches.

Sir James Learmonth, who writes a foreword to this volume, rightly praises Professor Mitchell's skill as a practical anatomist; we have too few in England to-day.

One of the features of this book is the excellence of the numerous illustrations; they are superb, and the photomicrographs are beautiful.

There can be no doubt that this book will make the lot of the medical student easier, for the whole anatomy of the autonomic nervous system has been written in a lucid and practical way and illustrated by pictures which are easy to follow.

Professor Mitchell has explained many queries of the sympathetic nerves, especially in the pelvis.

It is stimulating and refreshing to read a book of this calibre, for it makes one think and consider one's ideas relating to the autonomic nervous system.

It will long remain the reference volume on the subject.

Pathology of the Cell. By GORDON ROY CAMERON, M.B., D.Sc. (Melb.), F.R.C.P., F.R.S., Director of the Graham Research Laboratories and Professor of Morbid Anatomy at University College Hospital Medical School in the University of London. $6\frac{1}{2} \times 9\frac{3}{4}$ in. Pp. 840 + xvi, with Frontispiece and 64 plates and 41 illustrations in the text. 1952. Edinburgh: Oliver and Boyd. £4 4s.

AS the biological unit in pathology is the cell, this large volume deals in a most authoritative way with a really important subject. Although the history of pathology is as old as the history of medicine, yet this is the first comprehensive work dealing with the pathology of the cell.

This book is divided into four parts, the first dealing with the normal cell; the second with the abnormal cell; the third is concerned with a critical discussion of the cell theory; while the fourth sets out the author's ideas of cellular pathology of the future.

The book contains some excellent illustrations and some photographs of the early pioneers of pathology, including Walther Flemming, Max Schultze, Karl Virchow, and Ludwig Aschoff. Perhaps some of the best illustrations in the book are the photomicrographs depicting abnormal cells, such as the cholesterol-laden 'foamy' cells within a gall-bladder villus, and Gaucher 'foamy' cells in the liver.

The fourth part of this book gives a very excellent account of more recent work in pathology, especially new techniques and the value of the electron microscope.

The whole work must have been a labour of love and must have cost the author an enormous number of hours. It is a mine of information and will remain a reference volume for many years to come.

There is a very complete and accurate bibliography which should prove of great value to the pathologist.

There can be little doubt that this book will prove of value to all members of the medical and surgical profession who have an interest in pathology.

It must have been a great satisfaction to Professor Cameron that his old teacher and friend, Professor Charles H. Kellaway, saw the book before his death.

The Management of Abdominal Operations. Edited by RODNEY MAINGOT, F.R.C.S. $6\frac{3}{4} \times 9\frac{3}{4}$ in. Pp. 1253 + xvi, with 532 illustrations in 328 figures. 1953. London: H. K. Lewis & Co. Ltd. 120s.

MR. MAINGOT has undoubtedly edited another 'best seller' in his new volume devoted to the management of abdominal operations. He has gathered a team of 31 clinicians, mostly surgeons, who in turn have covered every aspect of the pre- and post-operative treatment of abdominal conditions. The physicians have also played an active part in this work. Dr. Avery Jones, in an excellent chapter, discusses in full the various conditions affecting the operative risk for abdominal cases. Maingot himself deals in a very practical way with the preparation of the good-risk patient and discusses post-operative care. Leslie Le Quesne gives experienced and sound advice regarding water balance, a subject of enormous importance to the modern abdominal surgeon.

Sir Cecil Wakeley writes on surgical diseases of the liver, while Milnes Walker covers the surgery of the spleen; both these articles show a matured clinical background.

Sir Gordon Gordon-Taylor is at his best in writing upon a subject he has made his own, namely, the management of abdominal injuries in warfare and in civil life.

The whole of this large volume is full of important practical information written by clinicians who are masters in their own particular fields.

The medical profession as a whole will be proud of this imposing volume, for it is indeed a credit to British surgery. The work will be of real value to the post-graduate who wishes to become *au fait* with abdominal surgery.

Surgeons both at home and abroad will find much to interest them in this great work of reference.

Die Angiographie. Zur Erkennung, Behandlung und Begertachtung peripherer Durchblutungs störungen. By Dr. Med. Habil. H. W. PÄSSLER, Leverkusen. $8\frac{1}{4} \times 12$ in. Pp. 115 + viii, with 102 illustrations. 1952. Stuttgart: George Thieme. DM. 29.70.

THIS book by Dr. Pässler, of Leverkusen, deals with angiography in the diagnosis, treatment, and prognosis of peripheral vascular disease. The angiograms are beautifully reproduced on art paper. Peripheral arteriography is fully covered as well as phlebography and abdominal aortography. The percutaneous femoral route is favoured for the lower limb as it allows repeated examinations when necessary. Translumbar approach in the way first described by dos Santos is used for aortography and a single film is exposed using the Bucky diaphragm. Attempts to make serial pictures and to include the vessels of the lower limbs as well as those of the abdomen have been unsuccessful.

The way in which angiography helps in treatment is described, so that there is much of interest in the book to the surgeon as well as to the radiologist. It is interesting to read of the post-war German attitude to operations such as arteriectomy and endarteriectomy and to find them very similar to our own. There are references to animal experiments and clinical results which throw doubt on the scientific basis and empirical results of arteriectomy. Endarteriectomy has not fulfilled the early hopes of many of its protagonists. Free grafts are favoured in selected cases for arterial thrombosis and there is a beautiful reproduction of an angiogram of one of Professor Fontaine's vein grafts two years after operation. A bank for homografts had not yet been established at Leverkusen because of organizational difficulties.